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<th>Category</th>
<th>Scheduled presentations (Abstracts)</th>
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<tr>
<td>Gastrointestinal (Noncolorectal) Cancer</td>
<td>4000 - TPS4154</td>
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<td>Genitourinary (Nonprostate) Cancer</td>
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<td>Head and Neck Cancer</td>
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<td>6500 - TPS6626</td>
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<td>8000 - TPS8058</td>
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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
ASCO Abstracts Policy

Public Release of Abstracts

The abstracts published in the 2017 ASCO Annual Meeting Proceedings, including those abstracts published but not presented at the Meeting, were publicly released by ASCO at 5:00 PM (EDT) on Wednesday, May 17, 2017. These abstracts are publicly available online through ASCO.org, the official website of the Society. Late-Breaking Abstracts, which include all Plenary Abstracts, will be publicly released according to the following schedule:

- 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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Conflict of Interest Disclosure

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.

ASCO offers a comprehensive disclosure management system, using one disclosure for all ASCO activities. Members and participants in activities use coi.asco.org to disclose all interactions with companies. Their disclosure is kept on file and can be confirmed or updated with each new activity.

Please email coi@asco.org with specific questions or concerns.
ABSTRACTS
American Society of Clinical Oncology
53rd Annual Meeting
June 2-6, 2017
McCormick Place
Chicago, IL

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 preclinical 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 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 eicosapentaenoic 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 E2 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 André 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 illustrated 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 preserving 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.
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

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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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

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 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.
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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 ProfiER Study. First Author: Olivier Tredan, Département d’Oncologie Médicale, Centre Léon Bérard, Lyon, France

Background: Routine molecular screening of advanced refractory 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. Alternative 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 were 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 listed in head 12 pts 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

<table>
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<th>Total Pts (n=54)</th>
<th>CIM for current</th>
<th>CIM with subsequent</th>
<th>No CIM due to poor performance status</th>
<th>No CIM due to lack of new target drug</th>
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<tr>
<td>N=54</td>
<td>22 (41.1%)</td>
<td>13 (24.1%)</td>
<td>10 (18.5%)</td>
<td>9 (16.7%)</td>
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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 NSG platforms. Observed modest increase in utilization of NSG 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 NSG identified many unanticipated PGVs of clinical importance for pts and their families.

Clinical trial information: HUM00067928.
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 Petylak, 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 4 cycles. Neutrophil–lymphocyte ratio was determined by IHC on 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: 41–89]) 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: 32–3000). 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 urininary tract infection (10%) and hypothyroidism (9%). No treatment-related deaths have occurred. Sixty pts had ≥1 post-baseline assessment. Antitumor activity was observed across the dose range; ORR (capable of confirmed disease response [CDR]) 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 antitumor activity in heavily pretreated mUC, including pts for whom CPIs have failed. Clinical trial information: NCT02091999.
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 BRAFV600 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% BRAFV600mutated; 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 varlitumab, 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.
Breast Cancer—Local/Regional/Adjuvant

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) vs 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.

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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, Istituto 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 ECx7 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-yr failure rate, cardiac toxicity, correllative 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%, IIIB 6.6%, III 2.1%. 30% of the pts had 3 lymph node positive nodes, 16% >=4. Sixty-eight% of 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 halved the rate of severe cardiac toxicity. Final DFS data will be available at the time of the meeting. Clinical trial information: NCT00629278.

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Oral Abstract Session, Mon, 9:45 AM-12:45 PM
Updated results from the phase III ALTTO trial (BIG 2-06; NCTCTG (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-T, 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 (TR), 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, 0.81-1.06; 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 L-T vs T-L. The differences for OS in L-T vs T-L 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, loco-regional, 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.

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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. SOLEx tested the hypothesis that 3 mos treatment-free intervals during extended trastuzumab adjuvant therapy will improve disease-free survival (DFS). Methods: SOLEx enrolled 4884 postmenopausal women with HR+ lymph node-positive BC who had completed 4-6 yrs of adjuvant estrogen therapy (19% SERM, 43% AI, 38% AI & 2% both; stratiﬁcation factors: histotype, grade, size, and node count). Participants were randomized to receive 3-6 yrs adjuvant 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 (randomisation 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 survival (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.

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504 Oral Abstract Session, Mon, 9-45 AM-12:45 PM
Prospective WSG phase III PlanB trial: Final analysis of adjuvant 4×EC×4 doc vs. 6×docetaxel/cyclophosphamide in patients with high clinical risk and intermediate-to-high genomic risk HER2-negative, early breast cancer.

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 6×CEF vs. 6×CMF in HER2+ EBC. prospective trials had 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 (Gluza et al. ASCO 2016).

Methods: The WSG Plan B trial was originally planned as a non-inferiority study comparing 6 cycles of anthracycline-free TC (Arm A) vs. standard anthracycline-taxane based chemotherapy (4×EC→4×Doc) (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 + 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 EC (n=1222) and 4x Doc (n=357). Within this cohort, 41% were pN+, 42% had G3 tumors and 18% HR-negative tumors by central pathology review. After median follow-up of 61 months, very similar five-year DFS of 89% (HR 0.88, 95%CI 0.71-1.11), 90.1% (0.92, 0.78-1.08) and 94.6% (0.96, 0.93-0.96) were observed in Arms A or 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 toward more Hematologic toxicity in Arm B (P<0.001). DFS 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.

Conclusion: In the WSG Plan B trial, patients with early HER2-negative EBC seem to be sufficiently treated by six cycles of docetaxel/cyclophosphamide compared to four cycles of EC followed by four cycles of doxorubicin/cyclophosphamide; 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.

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 further 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, 1.82×10^-3, max=+∞). 98/101 genes were mutated in at least one patient. Only variants in PI3K, 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 clinical-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 leveraging 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 cancer 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Surgery after initial lumpectomy to obtain a bigger negative margin is common and may lead to mastectomy. The impact of a 2014 margin guideline was addressed in this study. 

Methods: SEER registries were surveyed about 2 months post diagnosis, and 70% responded (97204 cases). The incidence of serious adverse events (SAEs) was compared between SB3 vs trastuzumab during the neoadjuvant period. Clinical trial information: NCT02162667.

Results: The ratio of bpCR rate was 1.259 and its 95% CI was 1.43-17.26; 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 common neutropenia, alopecia, and nausea; incidence of serious adverse events (10.5% vs 10.7%). PK equivalence was demonstrated between SB3 vs trastuzumab (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.
Breast Cancer—Local/Regional/Adjuvant

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 Hueber, 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. The 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 fluouracil, epirubicin and cyclophosphamide 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-yr EFS rate was 67%/67%/74% with L/T/T, respectively (Lv T HR 0.98 [95% CI 0.64-1.51] = 0.33; TL vs THR 0.81 [95% CI 0.52-1.26] = 0.35). In the hormone receptor negative group 6- yrs EFS rate was 61%/67%/68% for L/T/T, respectively (p=0.76; TL vs THR 0.81 [95% CI 0.44-1.51] = 0.52). OS at 6 yrs was 82%/79%/85% for L, T and TL, respectively (Lv T HR 0.85 [95% CI 0.49-1.46] = 0.56, TL vs T HR 0.72 [95% CI 0.42-1.27] = 0.23). In landmark analyses, pts with a pCR had significantly higher EFS (77%/85%) 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 cohort. Clinical trial information: NCT00533538.

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: Mehta Coban, 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 I-III breast cancer, but there is little data on how often it impacts patients’ preference for BCT versus mastectomy. The BrighTNess trial was designed to evaluate 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 clinicoradiographic criteria before and after NST; surgical management was at the surgeon and patient discretion. We assessed interactions between BCT eligibility pre- and post-NST, gBRCA 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-e at baseline, 75 (53%) converted to BCT-e but only 42 (56%) of these opted for BCT-e (p=0.005). BCT rates were 69% in BCT-e converts vs. 36% in those remained BCT-e. 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-e to BCT-e of 53%. BCT rates were lower in pts with gBRCA, the highest mastectomy rate among BCT-e pts in NA merits investigation. Clinical trial information: NCT02032277.

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

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 (NCT00741752) investigated the effectiveness of CT following local therapy for ILRR. Previously reported results at 5-yr 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 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-. Of these, 100 ER+ and 50 ER- patients were randomized to CT and 62 ER+ and 38 ER- patients to No-CT. After a median follow-up of 8.8 yrs, the primary endpoint OS was reached in 67% of ER+ and 74% of ER- ILRR patients. The OS rate in both ER+ and ER- ILRR was significantly lower in those randomized to No-CT compared with CT (HR 0.85 [95% CI 0.49-1.46] P=0.56). The DFS rate was 67% at 8.8 yrs in both ER+ and ER- ILRR, but there was a significant difference between treatment groups in ER- ILRR, but not ER+ ILRR. 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: NCT00741752.

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Breast Cancer—Local/Regional/Adjuvant

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 100142 (BT 213) MINDACT phase III trial.

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), q2wk 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 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, 950 pts to show superiority of PM(Cb). Secondary objectives compared pCR and DFS with PM(Cb). pCR rates of idd EPC compared to weekly PM(Cb) were not significantly different. PM(Cb) appeared to be less feasible. Clinical trial information: NCT00435389.

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, neo-adjuvant study of chemotherapy versus endocrine therapy in premenopausal patients with hormone responsive, HER2 negative, breast cancer (KBCSG 012).

First Author: Catriona Lin, Cardiff University, Cardiff, United Kingdom. First Author: Lee Jieun Cho, Seon Young Cho, Soo Young Jang, Seung Young Kim, Byung Hoon Lee, Eun Young Kim, Hee Seong Jang, Yoon Hee Han, Young Gyu Kim, Hee Jeong Kim, Department of Surgery, University of Ulsan, College of Medicine, Asan Medical Center, Seoul, South Korea

Background: Neo-adjuvant endocrine therapy has shown efficacy in hormone-responsive premenopausal 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 neo-adjuvant 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 neo-adjuvant chemotherapy with Adriamycin plus cyclophosphamide (AC) followed by taxane (T) or neo-adjuvant 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 neo-adjuvant treatment period (n=87, both). More patients in the chemotherapy group had no TILs after NAC (58% vs. 44%). TILs were assessed on H&E stained full sections of 120 pre- and 62 post-NAC tissues (tumor bed of NAC patients), with 35 patients included in both pre- and post-NAC trials. The mean TIL count was 11%; 5% had no TILs and 1.6% had 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 neo-adjuvant endocrine therapy had higher HER expression (all were more than 40% HER1 and 0% HER2). Conclusion: The efficacy and safety of chemotherapy versus endocrine therapy for hormone-responsive lymph node-positive premenopausal breast cancer patients has been demonstrated in this phase 3, randomized, double blind trial. The results suggest that neoadjuvant chemotherapy may be associated with higher DFS and lower rates of NAC-related toxicities, compared to endocrine therapy.

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

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 Schneeeweiß, University of Heidelberg, Heidelberg, Germany

Background: The sequential use of intense dose-dense (idd) epirubicin, paclitaxel, cyclophosphamide (EPC) and weekly paclitaxel/liposomal doxorubicin (Pm(Cb)) have been shown to improve DFS or OS, compared with standard anthracycline-based CT, including the C-high/G-high group. Safety profile of both regimens was as expected. Clinical trial information: NCT00435389.

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 Schneeeweiß, University of Heidelberg, Heidelberg, Germany

Methods: GeparOcto (NCT02125344) patients (pts) received 18 weeks (wks) either EPC (3× E 150mg/m² q2w followed by 3× P 225mg/m² q2w, q2w followed by 3× C 2000mg/m² q2w or PM(Cb) (12× P 80mg/m² plus M 20 mg/m² q1w, plus C 200mg/m² q2w). For HER2+ patients, breastconservation treatment (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 (24.5% vs 20.5%) were higher inAT. Cardiac events occurred in 9 pts overall, including 1 cardiac failure (AT), while 53 pts developed secondary cancers (13.2% vs 11.2%). Conclusions: Docetaxel-capecitabine did not improve DFS or OS, compared with standard anthracycline-based CT, including the C-high/G-high group. Safety profile of both regimens was as expected. Clinical trial information: NCT00435389.

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Background: Clinical studies suggest that TNBC is sensitive to DNA-damaging agents, including Cb, V or 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 (T2–4 N0–2 or T1 N1–2) amenable to surgical resection were randomized 2:1:1 to (Arm A) P 80 mg/m² weekly + Cb 6 mg/m² 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/m² or 600 mg/m² q2 or 3 weeks) × 4. Primary endpoint was pathologic complete response (pCR) in breast and nodes with >80% power at 2-sided α 0.05 using pair-wise comparisons for A vs B and A vs C to detect significant treatment effects using X² 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% vs p = 0.36), but pCR in Arm A was higher than Arm C (53.2% vs 31.0% vs p < 0.001). In non-prespecified analysis, pCR in Arm B was also higher than Arm C (57.5% vs 31.0% vs 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%/85%) 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 or Cb + P or Cb + P vs placebo. 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.
Breast Cancer—Local/Regional/Adjuvant

524 Poster Session (Board #124), 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 5-grade NIH-CAP 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 seven-hundred ninety-three 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 to control arm. At the time of this analysis all patients had completed CT. Hair preservation was observed in 34.8% in the CAP arm vs. 20.6% in the noCAP arm (p = 0.005). 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 showed 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 BC.

525 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-QOL was assessed at baseline (BL), every other week (EOW) and every cycle (EC). 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 clinicopathological 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 (44% vs 55% p = NS). The median score of fatigue after adjuvant therapy measured by QLQ C30 was lower in YCE (17.3 vs 22.2, p = 0.003) which was similar to that observed by BFI at 12-15mo (1.06 vs. 1.04). Also in YCE there was lower reporting of detriment in general activity (41% vs 59% and mood (34% vs 66%) (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, least costly complementary therapy that may improve compliance by improving parameters that can affect day-to-day activity in women with breast cancer. Clinical trial information: NCT02161900.

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Refined estimates of local recurrence risks and the impact of the DCIS score adjusting for clinico-pathological features: Meta-analysis of ES194 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) after breast-conserving surgery (BCS) for DCIS to inform treatment decisions. The DCIS Score (DS) was validated as a predictor of LR in ES194 and Ontario DCIS Cohort (ODC) after BCS without radiation (Solin, 2013; Rakovitch, 2015). We performed a meta-analysis (MA) combining data from ES194 and ODC with additional follow-up from ES194 adjusting for pertinent clinico-pathologic factors to provide refined prediction estimates of LR risk after BCS alone.

**Methods:** The MA used data from ES194 and ODC. Patients with positive margins and multifocality were excluded. Identical Cox regression models were fit including age at diagnosis (< 50, 50-69, 70+ yrs), tumor size (1 cm, >1 cm), 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% ES194, 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<0.009). Hazard ratios from ES194 and ODC cohorts were similar for tumor size: 1 cm = vs. > 1 cm (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 high risk DS is associated with a higher 10 yr predicted risk of LR in all LR risk estimates to guide individualized treatment decision-making.

**Conclusions:** Refined estimates of local recurrence risks and the impact of the DCIS score adjusting for clinico-pathological factors to the DCIS Score provides enhanced prognostic discrimination.

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 Soyan, 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 to 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 (≤ 40). We evaluated the long-term outcome of HER2+ breast cancer patients ≥60 year old and compared with those ≥50 yr. Pt from N9831 trial were evaluated.

**Main Findings:** In 538 women who initiated ET and continued for at least 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. Among 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 multivariate analyses (OR: 1.85, 95% CI: 1.05-3.26, p = 0.03). 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. Aims: As part of a prospective cohort that enrolled women with BC diagnosed (dx) ages 40-70 during 2006-2013, we identified 1103 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 any hormone therapy and/or who stopped H at 3 yrs post-diagnosis (or last follow-up if < 3 yrs) were classified as non-persistent. Code: [**531**]
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-II 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 566,075 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 (cT: 4.5% 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<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 outcomes in TN MBC, but the 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 (7.6% 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 in other investigations, and development of MBC-specific guidelines could potentially improve treatment standardization and outcomes.

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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% NO, 88% grade 3, and 75% had Ki67 > 15%. Histologically, 39% were anaplastic, 26% invasive ductal, 16% medullary, 8% metastatic, 6% apocrine and 5% others. Median sTILs were 20% (9-0%) 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 (metastatic subtype) was associated with better IDFS, HR+/HER2+ (HR 0.35, 0.01-0.89), however 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 as contrast to the full cohort, a lower proportion of TN MBC patients received chemotherapy (7.6% vs 78.7%, p = 0.008) and ALND (35.2% vs 38.2%, p = 0.01) vs TN non-MBC patients. Conclusions: BC had worse OS vs non-MBC, and unlike other histologies, outcome was not driven by receptor status. Multimodal therapy improved outcomes in other investigations, and development of MBC-specific guidelines could potentially improve treatment standardization and outcomes.

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534 Poster Session (Board #134), Sun, 8:00 AM-11:30 AM
Prospective study of magnetic resonance imaging (MRI) and multparameter 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, were entered into the E4112 trial. Those with clinical T stage T1a with negative margins and non-anaplastic DCIS were eligible. Study patients were randomized to MRI and DCIS Score on surgical and RT management. MRI was performed 2-4 weeks after BCS. If MRI evidence of local recurrence, therapy was modified according to the DCIS Score on surgical and RT management. MRI. Those remaining so following MRI and related biopsies, with no inoperable disease, underwent BCS. If final surgical margins were 2 mm, the 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 Score was obtained on 171 patients who completed BCS, of whom 82 were LS and 89 were HI. Demographics were similar between the two groups, other features will be reported. Of these, 43% had no DCIS Score was assessed for 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.
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 0.90-1.81; p=0.19 Cox regression analysis) without uPA expression. No such association was observed for PAI-1 and for the uPA/PAI-1 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 (85.0% vs 77.3%; p=0.010) 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 of b evidence for a prognostic role of stromal uPA in women with endocrine-responsive early breast cancer.
Background: We previously reported the cardiac safety results 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

Methods: Patients were enrolled with HER2 overexpressed (immunohistochemistry 3+) or amplified (fluorescence 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 ddAC (60/600 mg/m2) 2 weeks (w) x 4 - 1.75 mg/m2 q 2 w x 4 with H (loading dose 4 mg/kg - 2 mg/kg q w during T - 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, 23% 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% had hormone-receptor positive disease, 11% (16%) had T3 disease, regardless of size or nodal status, respectively. 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), 1.3%-7.7%). The 9 and 10 year DFS rates were 89% (95% CI, 78%-94%) and 87% (95% CI 75%-93%), respectively. Conclusions: Long-term follow-up of this study has demonstrated that ddAC TH is associated with a low risk of CHF and promising DFS in patients with early-stage HER2-positive breast cancer.

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 treatment/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 NO/N1 mi/N1 disease who were RS-tested from 1/2006 (CHS approval of the test) through 12/2010 (NO) or 12/2011 (NO/N1/mi/N1). Medical records were reviewed to verify treatment/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 5.7 (0.9-9.6) yrs, respectively. Of 2,047,868 patients, chemotherapy receipt and oncologists' 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 recommendations, 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-negative 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 more likely to give 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.

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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/FLI1/78 (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 clinicalpathologic and molecular variables from cases submited 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% <64y (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 < 0.01 for all). In pts ≥75y, BCI identified 33.9% 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 morbidities and potential toxicities from therapy.

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 breast 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 clinical 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 (t), 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 useful for high risk cases requiring chemotherapy. With further validation, our model could provide a clinically useful estimation of high risk at lower cost.

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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 2005-2014 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 (pN=83%) or I-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, young, non-high school 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 = 0.89, 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.
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: Tristan Sinane 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 42,571 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 (1-3 positive sentinel nodes), SLNB alone was associated with a significantly increased risk of all-cause mortality compared to ALND or SLNB+RT. These results suggest 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: SenSzl (GBG80) trial.
First Author: Sherko Kummel, Breast Unit, Klinikum 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 cT0 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. Primary 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: Pembrolizumab 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 before treatment. 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), defined as ypT0/Tis, ypN0, and ORR (RECIST v1.1, investigator). pCR analyses included all end points were pathological CR (pCR) rate, defined as ypT0/Tis, ypN0, and ORR (chemo + pembro; 1 DVT with chemo). Overall ORR (CR+PR) before surgery were fatal. One pt in A and 2 pts in B discontinued for a TRAE (2 ALT elevations with pembro; 1 DVT with chemo). 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. Primary 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.

557 Poster Session (Board #157), Sun, 8:00 AM-11:30 AM
Primary operation in synchronous 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 or chemotherapy or both. The preoperative LSG was performed 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 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 significantly 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-ABCSCG-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.

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Breast Cancer—Local/Regional/Adjuvant

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 <2 mm. 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 ≥2mm 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 <2mm 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=0.001). 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 optimized 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 (ypNo vs. ypN+) in patients converting from cN+ to ycN0 through primary systemic therapy (PST). First Author: Cornelia Liedtke, University of Schleswig-Holstein Campus Luebeck, Luebeck, 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 (1.01; 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 ypNO ypP+ 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; 1.01-1.07). 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.

561 Poster Session (Board #161), Sun, 8:00 AM-11:30 AM
Auxiliary 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 what drives overtreatment. 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 for patients undergoing lumpectomy in older women with stage 1 ER+ breast cancer, radiotherapy is commonly administered, raising concerns about overtreatment. Therefore, we sought to evaluate physician attitudes, knowledge, communication, and reasons for recommendations in this scenario. Methods: We mailed surveys identified by the sentinel node study (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 28% of surgeons were elderly (≥65) or low users (83%; p=0.06) of ALND. Surgeon age (p=0.08) and SN positivity (p=0.04) were associated with the opinion that radiotherapy omission is unreasonable. 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: 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 (1.01; 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 ypNO ypP+ 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; 1.01-1.07). 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.

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Background: Lymphedema (LE) is a serious complication of axillary lymph node dissection (ALND) with an incidence rate of 16%. Lymphatic Microsurgical Preventing Healing Approach (SLYMPHA) 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 efficacy 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 15.7 ± 13.7 (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.
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 Harvad 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 40/2.6 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 to see significant differences. Good cosmesis 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 = 0.0294). Conclusion: 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.

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, different treatment 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% IB, 10.8% IIB, 18.3% IIIA, 7.2% IIIB. A total of 585 patients were 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.

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: Ajay Bulbul, Kymere 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 and bilateral irradiation. 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 I-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 multivariable logistic regression. Results: Out of 533 patients, 510 (92%) had early stage (0-3) resectable BC. Among these, 48% (246/510) had either MRM (205/510) or SM (37/510). MRM was performed in 3% of stage 0 (6/209), 23% (49/209) stage 1, 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 CBT were 2.15 (95% CI: 0.28-15.0) and 0.50 (95% CI: 0.12-2.02), respectively. At median follow up, the predictive probabilities of lymphedema after BCT, SM, MRM and BM were 1%, 4%, 9% and 18%, respectively. The OR for local recurrence in women with BCT were 1.46 (95% CI: 0.72-2.95), SM 0.27 (0.03-2.13), BM 2.06 (95% CI:0.70-6.36). Conclusions: Less BCT and more aggressive surgical 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 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.

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Poster Session (Board #172), Sun, 8:00 AM-11:30 AM
Safety of MEDI4736 (anti-PD-L1 antibody) administered concomitantly 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 anti-PD-L1 therapy. 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 treatment 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 gr 1 within 14 days, (3) > gr 3 colitis or pneumonitis, (4) > 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 recurrence 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 withdrew 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 is safe. The Phase II portion of the trial is open to accrue a maximum of 50 patients to assess the efficacy of the combination.

Clinical trial information: NCT02489448.

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Poster Session (Board #174), Sun, 8:00 AM-11:30 AM
Antitumor activity of trabectedin and lurbinectin 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 at different levels. Having 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 lurbinectin (L), have shown to be active in BRCA 2 associated 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%/55.9%/26.2%; L, 55.9%/47.2%/26%). 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 lurbinectin as single agents was observed in BRCA2 associated MBC. This finding warrants further investigation. One potential mechanistic rationale is the role of markers (proliferation score and ROR scores, MKI67, CDC20, NUF2, KIF2C, CENPF, EMP3, TMY3) were positively associated with pCR (p<0.05 for all).

Within the germline, angiogenesis genes were negatively associated with pCR (ANGPTL4: p=0.05; FGFR4: p=0.02; VEGFA: p=0.03). In the whole collective, basal-like (83.3%) was favorable for pCR (38% vs. 20%, p=0.015) compared to other subtypes (HER: 6.4%; luminal-A: 17.6%; normal: 8.7%), as was lower HER-2 score (p<0.001). Proliferation was positively associated with 100 proliferation scores (all p<0.004), and higher Ki67 by central IHC (p=0.015) – 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 improved pCR. This points to the need for new chemo-sensitivity for both neoadjuvant arms. Chemo-resistance pathways differed between the two taxane-based combinations (low proliferation and immune marker gene expression for carboplatin, high angiogenesis for gemcitabine). 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.

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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 subtype. 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 anthracycline and taxane regimens (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. Conclusion: 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 the results are observed with newer agents, such as platinum, PARP inhibitors and other targeted agents.

Methods:
Outcomes of AC versus NAC in pts with early stage TNBC with and without BRCA germline mutations were compared by stage I and II. Further studies are needed to analyze outcomes of AC versus NAC in pts with early stage TNBC with and without BRCA germline mutations. Conclusion: No association was observed 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.

Methods:
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/m²) x 12 followed by FE75 mg/m² x 3 and neoadjuvant chemotherapy. Results: 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-II, 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. Conclusion: 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 was substantiably lower in ER- cancers. Clinical trial information: NCT01855828.
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-IIII 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-IIII 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/N0. Univariate/multivariate logistic regression and chi-square 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%, odd 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 was 62% vs. 55% (stage Ivs. 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, 2.6; C-no, OR = 1.8) (P = 0.30 for interaction). Of 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 < 0.0001). 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 HER2+ 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 databased 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 NET was compared to NACT. 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, the CPS+EG score 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 Eichtler, Krankenhaus Köln-Holweide, Cologne, Germany
Background: Trastuzumab (T) and Lapatinib (L) containing neoadjuvant chemotherapy (NACT) increases pathological complete response (pCR) (vs. T or nill) in HER2+ early breast cancer (BC). Clinical early 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 pCR response in a dual blockade (T+L)-NACT setting. Methods: Patients with cT1c-cT4c HER2+ EBC were treated by paclitaxel (P) (80 mg/m² weekly) with L (750 mg p.o. daily) + T (2 mg/kg) weekly for 12 weeks. Adjuvant treatment with 4 cycles of Epirubicin/Cyclophosphamide (e/c) and Taxane at 200 mg/m² weekly was recommended. Primary objectives were pCR (yTP0/ySp0/yPD) 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 was a substantial number of patients and negative DFS data from the ALTTO trial did not identify trial continuation. 27% of patients had early 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 monochemoherapy 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: 2012-036379-21.

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: Niambi 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) chemotherapy. Of the 78 patients, 24 consented to an optional on-treatment biopsy 20 days after cycle 1 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 Haemotoxylin+Eosin, AE1/AE3 and CD45 in formalin fixed paraffin embedded samples (FFPE) baseline biopsies and on pre-treatment sample pairs and then used the Microenvironment Cell Populations (MCP)-counter method to measure the abundance of 10 immune cell populations (T cells, C8B 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 TCHL based therapy. We found in day 20 on-treatment biopsy 4% of women that subsequently went onto have a pCR. However, of patients with mutations in other genes we found 9% of patients with TILs 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.
Conclusions: Obesity not only increases morbidity, but also chemoresistance 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 DDPS 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 DDPS (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.
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 UMIN000005586. Clinical trial information: UMIN000005586.

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

NRG Oncology/NSABP B-51/RTGOG 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 (IBCRF) in patients (pts) with positive axillary (Ax) nodes who are young 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 IBCRF rate in pts with Ax+ 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 Pdx pts (FN/A 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 pts is performed. ER/PR and HER2-neu 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 IBCRF 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 Clinic Coord Dpt: 1-800-477-7227 or cccfrsab.org. Support: U10-CA-2166; -180868; -180822; 189867; Elekta Clinical trial information: NCT01872975.

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Breast Cancer—Local/Regional/Adjuvant

**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 Baggini, 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 naive 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 potent inhibitor 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, and 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 C4028. 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 (15% vs 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 in the study and have 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 thereafter, 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.

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**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) 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 both) 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 measures. A total of 165 pts were planned for safety and efficacy endpoints. A total of 165 pts were planned for safety and efficacy endpoints. 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 prior ET resistance, and 82% were postmenopausal. The observed increase in PFS and OS, safety, and correlative biomarker studies. A total of 165 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 an efficacy endpoint in patients with HR+HER2- advanced breast cancer who progressed on endocrine therapy with significantly improved PFS and ORR. Clinical trial information: NCT02107703.

Conclusions: Abemaciclib + fulvestrant in patients with HR+HER2- advanced breast cancer who progressed on endocrine therapy showed clinical activity as abemaciclib + F, 378 events were needed for 90% power at one sided α=0.025. 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 prior ET resistance, and 82% were postmenopausal. A total of 165 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 both) 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 measures. A total of 165 pts were planned for safety and efficacy endpoints. 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 prior ET resistance, and 82% were postmenopausal. 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 (84.6% 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 in patients with HR+HER2- advanced breast cancer who progressed on endocrine therapy showed a statistically significant OS benefit, median OS 20.7 months with abemaciclib + fulvestrant vs 17.7 months with P + fulvestrant (HR = 0.69, 95% CI 0.4 - 1.1, p-value 0.13, exploratory). AEs were in line with previous data.

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**Overall survival results from the randomized phase II study of palbociclib (P) in combination with letrozole (L) vs letrozole alone for front-line 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 was increased with addition of P to L (20.2 mos vs 12.0 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 PFS as part of the study. **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 27.5 vs 33.5 mos (HR = 0.837; P = 0.290) for Part 1 and 35.7 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.

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**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 of HER2-targeted therapy + AI improved clinical benefit in patients (pts) with HER2+, HR+ MBC 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 Q2W)+L (1000mg/d)+AI or T+AI or L (1500mg/d)+AI. AI was per investigator 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). 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 (PFS 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%, 15%, and 14% respectively) were diarrhoea (69%, 9%, 5%), rash (36%, 2%, 26%), 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 AEs was 5%, 2%, and 2% and on-tx deaths was 3%, 4%, and 5%, respectively. **Conclusions:** Dual HER2 blockade with L+T was superior to single HER2 blockade (T and L) in pts without previous exposure to HER2-directed tx with 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 genomic data using a Bayesian algorithm.

**Background:** Negative breast cancers (TNBCs) are lacking. We sought to classify TNBCs 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 classification of 7 TNBC subtypes. Pts were assessed 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 assessed by RECIST. Results were compared to the BL1 TNBCtype-4 subtype and assessed using a multinvariate 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 C6, 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 M6-TNBCs (61%, OR = 1.19, 95% CI = 0.37 to 3.81, P = 0.79) had RCB0. Similarly, 65% of the BL1-TNBCs had an RCB0, however in a smaller population (11 out of 17, OR = 1.30, 95% CI 0.35 to 5.31, P = 0.77). In Sarcoma Phase III, the objective response rate (ORR) in M6-TNBCs was 46% versus 30% in non-M6-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 or MEX inhibitors in relation to this signature.

**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, EGF/ 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 3 had CNS progression after local CNS tx. During 21 day cycles, pts received capecitabine 750 mg/m2 twice daily for 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 2nd stage; 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 metastasis lines 2 (range 0-6). Of 39 pts, 8 (21%) were BRCA1/2. AEs of grade 3 or 4 in 15% of pts 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 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 investigation of the regimen for BCBM. Updated results will be presented at the meeting. Clinical trial information: NCT01494662.
Background: In KEYNOTE-012, pembrolizumab showed durable activity and manageable safety in patients (pts) with PD-L1-negative mTNBC. Cohort A of KEYNOTE-012 examined efficacy/safety of pembrolizumab in mTNBC, regardless of PD-L1 expression. Methods: Pts with centrally confirmed mTNBC <5 years prior to start of pembrolizumab for metastatic disease, and ECOG PS 0–1 were randomized 2:1 to pembrolizumab 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 pembrolizumab 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 pembrolizumab. 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 survival was 6.0 (95% CI 3.9–8.1) mo; no 12-mo survival was observed. mTNBC, regardless of PD-L1 expression.

Lotus (NCT02162719): A double-blind placebo (PBO)-controlled randomized phase II trial of first-line ipatients and mTOR pathway (mTORC1 and mTORC2) inhibitor, everolimus (EVE, 5 mg daily), in patients (pts) with HER2+ metastatic breast cancer (mBC)

Background: Lotus (NCT02162719) examined the efficacy/safety of pembrolizumab in previously treated mTNBC, regardless of PD-L1 expression.

Background: Post hoc analyses (17 June 2016) were conducted of randomized trials that evaluated everolimus (EVE) plus endocrine therapy in patients with estrogen receptor (ER)–positive, human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (BC) including First- and second-line data from the BOLERO-4 study, which evaluated EVE plus 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 data (median follow-up 14 months) from the BOLERO-4 study (NCT01698918). Methods: Eligible pts had one to three prior lines of chemotherapy for metastatic disease and ECOG PS 0–1 who progressed on 1L EVE + LET received optional 2L EVE + EXE. 2L data, although limited by the small number of pts, showed promising activity. While intracranial RR to EVE was low (12%), who progressed on 1L EVE + LET received optional 2L EVE + EXE. Median RR was 46% and median TTP was 4 mos (95% CI, 2.2–9.2). CNS CBR (6 mos) was 27%; CNS CBR (3 mos) was 65%. Extracranial RR was 46%; Median TTP was 3 mos (95% CI, 2.2–5). OS was 11.2 mos (95% CI, 8.0–14.5). The efficacy of 2L EVE + EXE was consistent in the prespecified subgroup with PIK3CA/AKT1/PTEN alterations, warranting further evaluation of IPAT in these pts. AEs were manageable. Clinical trial information: NCT02162719.
Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA (ctDNA) in metastatic breast cancer. First Author: Charlotte Victoria Fribbens, Royal Marsden, 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 sequencing samples from 34 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 progression, and at first line AI therapy switch. 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.
Genomic profiling of circulating tumor DNA (ctDNA) from patients 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 256 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(-)/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 *PIK3CA* (39%), *ESR1* (36%), and *TP53* (35%). 69 ER+ pts 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 driver GAs were *ESR1* (Y537S/N (n=47)), *PIK3CA* (E380Q (n=7), rearrangement (n=3) and amplification (n=1) were also observed. Concurrent GA with *ESR1* were found in *PIK3CA* (41%), *FGFR1* (13%), *BRCA1/2* (5%), *HER2* (5%) and AKT3 (7%). In ER(-) pts, the most common GA were in *TP53* (47%), *PIK3CA* (17%), *NF1* (11%), *BRCA1/2* (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 82% of cases. *PIK3CA* and *ESR1* mutations were identified in 22% of cases with ctDNA ctDNA assessment may predict sensitivity to palbociclib and fulvestrant, and if early loss of *ESR1* GA was associated with resistance. Kinase fusions in *PIK3CA* and *ESR1* may be complementary approaches to tissue-based genomic testing for pts with mBC.

Predicting sensitivity to palbociclib with early circulating tumor DNA dynamics in the PALOMA-3 trial. First Author: Ben O’Leary, Royal Marsden Hospital, 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 early circulating tumor DNA (ctDNA) dynamics that could predict clinical outcome on palbociclib (Palbo) and fulvestrant (Fulv). 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 (dPCR). Key objectives were to evaluate whether ctDNA levels of PIK3CA and ESR1 mutations were: (1) higher in ER+ patients than in ER- patients; (2) correlated with PFS; (3) different between treatment arms; and (4) predictive of progression. Results: PIK3CA mutations were identified in 22.0% (100/455) of screened baseline samples with 52 of these randomised to Palbo + F and 48 to Fulv. Variation in PIK3CA ctDNA was observed in 89% of cases. 24 pts had >1 PIK3CA GA; all pts with PIK3CA GA had prior AI. 24 pts had >1 PIK3CA GA, with instances of GA in cis. Frequent driver GAs were Y537S/N (n=47), D538G (n=29) and E380Q (n=7); rearrangement (n=3) and amplification (n=1) were also observed. Concurrent GA with PIK3CA were found in *PIK3CA* (41%), *FGFR1* (13%), *BRCA1/2* (5%), *HER2* (5%) and AKT3 (7%). In ER(-) pts, the most common GA were in *TP53* (47%), *PIK3CA* (17%), *NF1* (11%), *BRCA1/2* (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 82% of cases. *PIK3CA* and *ESR1* mutations were identified in 22% of cases with ctDNA ctDNA assessment may predict sensitivity to palbociclib and fulvestrant, and if early loss of *ESR1* GA was associated with resistance. Kinase fusions in *PIK3CA* and *ESR1* may be complementary approaches to tissue-based genomic testing for pts with mBC.

Abeemaciclib 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:** Abeemaciclib 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). Abeemaciclib has been shown preclinically to cross the blood-brain barrier (BBB) and has shown clinical activity in patients with BM (BM) in a Phase 2 trial. Methods: Study I3Y-MC-123 is an open-label, Phase 1 dose escalation study in pts with HR+/HER2- MetBC. 39 pts were enrolled to Stage 1. Safety, tolerability, and PK of abemaciclib were also assessed. Stage 1 includes 23 pts; if > 2 of the 23 pts respond to abemaciclib, if ≥2 respond, 33 pts are 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 non-evaluable, 2 pts (8.7%) had confirmed partial response (PR) in the Safety analysis. The 33 pts that were enrolled to Stage 2 were aged 45-72 years, with a median ECOG performance status 1. The most common grade 3/4 toxicities were decreased appetite (12 pts, 37%), fatigue (10 pts, 29%), nausea (8 pts, 24%) and vomiting (7 pts, 21%). Median PFS was 12.26, p = 0.0002). Overall, Palbo + F suppressed D15 ctDNA levels of abemaciclib similar to plasma were detected in resected BM in a subset of pts with HR+, HER2- MBC in a study. Methods: Study I3Y-MC-JP029. 33 pts were enrolled to Stage 2. Efficacy evaluation was performed after 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 (21 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 has the potential to penetrate BM in pts with HR+, HER2- MBC and did antitumor activity in this population. Final results will be presented following Stage 2 analyses. Clinical trial information: NCT02308020.
Efficacy of trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (MBC) previously treated with pertuzumab (P). First Author: Ander Urtubiocechea, Onkologiska Föreningen, 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; however, 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 II/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 vs P + H while PHEREXA studies H + capcitabine (C) vs P + H in pts who previously received P + H. Patients who received T-DM1 at any time after discontinuing study-assigned H or C were included in the analysis.

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.

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<th>Arm</th>
<th>No. of pts (95% CI)</th>
<th>No. of events (95% CI)</th>
<th>OS (95% CI)</th>
<th>PFS (95% CI)</th>
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<td>7.1 (4.9-9.4)</td>
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<td>HCP</td>
<td>130 (42)</td>
<td>31 (11-48)</td>
<td>16.8 (9.8-24)</td>
<td>7.2 (4.0-9.9)</td>
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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, with findings of real-world implications. Clinical trial information: NCT00567190, NCT01026142.

Circulating PD-L1 (programmed death-ligand 1) and outcomes in a HER2- postmetastic 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 outcomes in a HER2-negative breast cancer cohort treated with trastuzumab. Methods: Pretreatment serum PD-L1 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. 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 highest quartiles of serum PD-L1 were also more likely to have reduced PFS (p = 0.015) and 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-negative 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.
Breast Cancer—Metastatic

1025 Poster Session (Board #17), Sun, 8:00 AM-11:30 AM
Erubulin 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/m² every 3 weeks in MBC patients is difficult. Erubulin (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 (UMIN00012232). 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/m² 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 reached. The 6-month 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 events (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 and be safe in HER2-positive MBC. Clinical trial information: NCT00012232.

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: Sanika 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 PI3Kα 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; cohort 2: 250 mg) and T-DM1 3.6 mg/m² 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 (0.3–19.1). Median PFS was 6 months (95% CI 2.9–10.6). In 11 pts without prior T-DM1, PFS 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 kinase 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 kinase reprogramming (AKRP) is a resistance mechanism to kinase-targeted therapy (Rx) in TNBC (Cancer Discover-y2017). We studied AKRP in HER2+ BrCa by comparing transcriptome and kinase profiles before and after Rx with FDA-approved anti-HER2 drugs and combinations: trastuzumab (T), pertuzumab (P), T+P, or T+ lapatinib (T+L). Kinome profiling from 11 pts (3 T, 3 P, 4 T+P, 2 T+L). Methods:му Kinome response profiling from 11 pts (3 T, 3 P, 4 T+P, 2 T+L) and combinations: trastuzumab (T), pertuzumab (P), T+P, or T+ lapatinib (T+L). Methods: RNAseq. Kinome response profiling from 11 pts (3 T, 3 P, 4 T+P, 2 T+L) and combinations: trastuzumab (T), pertuzumab (P), T+P, or T+ lapatinib (T+L). Results: Two hundred HER2-negative cases (7.2%) were classified differently with 1 plus P was well-tolerated and could be an alternative to docetaxel and be safe in HER2-positive MBC. Clinical trial information: NCT00012232.

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-Ircs, 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 dual-color FISH. First Author: Elisa Gasparini, Breast Unit Arcispedale S. Maria Nuova-Ircs, Reggio Emilia, Italy

Results: Two hundred HER2-negative cases (7.2%) were classified differently based on the AC2013: 0.3% (2/7278) 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%/1%, 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 bellite the clinical impact of AC2013 HER2-equivocal reclassification; accordingly future studies are necessary to justify this category and the reclassification efforts by additional reflex tests.

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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 Health Care Institute, Department of Population Medicine, Boston, MA

Background: 80% of workers have high-deductible health plans (HDHP) that require major out-of-pocket (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 through a large national health plan. We included 7142 women aged 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) 2004-2012 calendar trends in total annual OOP spending, (2) monthly total OOP spending in the last 6 months before and after diagnosis, 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 (113.205.2). 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 $289.7 per person month among low-plan ($171.4 per 2 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.

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, Daichi Sankyo Co., Ltd., Tokyo, Japan

Background: DS-8201a, a HER2-targeting antibody–drug conjugate (ADC), with a topoisomerase I inhibitor, exetane dextrate (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 assessed in a syngeneic mouse model of 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 cells. 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. Also, in a syngeneic model, 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 estimation of 3-yr observed survival (OS) were compared across 8 models with a topoisomerase I inhibitor, exatecan drivative (DX-8951 derivative, DXd) and a PI3-kinase 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.

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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. Iyerang, 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 <3 prior chemotherapies. Pts received G (1200 mg/m²) on days 1 and 8 of a 3 week (w) cycle, and H (8 mg/kg) load → (6 mg/kg) and P (840 mg load → 420 mg) on w3. 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-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 1.27–1.41, 46 pts 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/m².

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.

Her2-positive metastatic breast cancer (MBC) after prior pertuzumab-based therapy. 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 HER+ ABC. However, ET resistance is 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 1:1:1 toRIB (600 mg/d, 3-weeks-on–2-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^-6. 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 pts 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% (HR = 0.589; 95% CI 0.44–0.788). The results were consistent across pts subgroups. The most common Grade 3/4 laboratory abnormalities (≥10% of pts; RIB + LET vs PBO + LET) were decreased neutrophils (62.6% 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 RIB + LET persists in postmenopausal women with HR+, HER2– ABC. The study remains immature for OS analysis. The safety profile of RIB + LET analysis manageable. 1. Lee C. P, Tobagyi G, et al. N Engl J Med 2016;375:1738-48. Clinical trial information: NCT01958021.
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 cancer (rMBC) (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 (AI) 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 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 CTC AE 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 23-67). The median TTP was 17.2 months (range 8.0-55.0). The median TTP was 7.2 vs. 25.3 months, one-sided P = 0.048, A+G vs G (95% CI 1.0-9.8). For the comparison of each experimental arm to control arm, 24-mo TTP were analyzed: F+G vs G (HR = 0.61; 95% CI 0.37-0.99); F vs A (HR = 0.45; 95% CI 0.23-0.87); F vs G (HR = 0.57; 95% CI 0.30-1.08). The median TTP was 17 months (95% CI 14-21.5, median 17.2, 7.2 vs. 25.3 months, 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 = 0.015 and 0.015, respectively).

Conclusions: The combination of F+G as well as A+G may be a valid option for HR(+) premenopausal women with T-pretreated MBC and further investigation is warranted.

Clinical trial information: NCT01266213.

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. ER1), 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 metastatic MBC. The 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 patients were enrolled and included aromatase inhibitors (37/38, 97%), fulvestrant (22/28, 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.]) was 26.3% (95% CI: 13.4-43.1%). cfDNA was obtained from 36 pts and mutations were identified in 13 (36%) including ESRI [1537N or 353R (5), PIK3CA [H1047R or E542K (2), TP53 [K132R, R248Q, R248Q, or K179R (4), AKT (Q79K) (1), and KRAS (G12D) (1)]. In 5 pts with cf ESRI 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 PFS 7 vs. 32 months, 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 ER1, 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, further investigation is required to determine which approach maximizes prognosis and prediction of benefit for estrogen-targeted therapy. Clinical trial information: NCT01327781.

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)+ BC. Methods: A 3+3 dose escalation phase Ib 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 the maximum tolerated dose (MTD) and 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 44-76; previous tamoxifen, 10 pts). Mean lines of prior therapy for metastatic BC was 2.5 (median, range 0-6) and included tamoxifen (6 pts). ESRI mutations were present in cfDNA 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 partial disease response and 5 (38%) had stable disease (range 61 to 132 days, median 69 days). 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, cfDNA and PET scans is ongoing to gather additional data, future studies are ongoing to determine the 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 therapies involving CDK4/6 or mTOR inhibitors have similar efficacy but vary in tolerability among older and younger patients with HR+, HER2– ABC. For combination therapy 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 at University of Nottingham, Royal Derby Hospital Centre, Derby, United Kingdom.

Background: 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 1st-line 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 therapy 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 at University of Nottingham, Royal Derby Hospital Centre, Derby, United Kingdom.

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 therapy in patients with HR+, HER2– ABC. 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.

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 1st-line 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 therapy 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 at University of Nottingham, Royal Derby Hospital Centre, Derby, United Kingdom.

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 therapy in patients with HR+, HER2– ABC. 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.

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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+/HER2-negative metastatic breast cancer (MBC) patients (pts): Dream or reality? Evaluation of a composite risk score in a subpopulation of the GIM 13-AMBRA study.

First Author: Giorgia Mustacchi, University of Parma, Parma, Italy

Background: The appropriate choice of 1st-line therapy in HR+/HER2-negative 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 approved "composite score" (Schimid, 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 response rate, according to the mentioned score in a population of HR+/HER2-negative MBC pts.

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 2015 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 listed 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.

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

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

Background: For HR+/HER2-negative 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 a treatment for a newly diagnosed mBC between January 2008 and December 2010 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). Survival curves 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-negative 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, 37-96). 53.9% of pts had visceral and 80.1% non visceral disease at diagnosis. Median OS of HR+/HER2-negative mBC pts (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-negative mBC pts (median age 62.0 years [range 23-96]). 53.9% of pts had visceral and 80.1% non visceral disease at diagnosis.

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+ve ABC with visceral recurrence. Biomarker analyses are ongoing in pts with long-term benefit to understand the molecular features which could be predictive of survival benefit.

Funding: Pfizer. Clinical trial information: NCT01942135.

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

1049 Breast Cancer—Metastatic

1050 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 second-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 186 HER2-ve ABC patients (1). A Bayesian pharmacokinetic (PK) analysis was conducted to estimate PAL PK parameters for individual Pts. Average concentration of PAL over the entire treatment (Cavg) was derived from average daily dose intensity divided by post hoc PK estimates of clearance (CL/F). Time vector for Cavg 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 Cavg, Cmax, 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 Cavg were similar (9.47 and 10.9 months, respectively) and significantly higher than that of the control arm (4.57 months). While Cavg was found to be a significant predictor for PFS in univariate analysis (P-value < 0.05), this relation in the multivariate analysis was not significant. 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.

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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 < 3 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 defined as a complete response (CR), partial response (PR) or stable disease at least of 24 weeks. Results: 23 patients with mean age 67 years (42 to 81) were identified. 95% were postmenopausal, 81% 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 Meister estimate showed median PFS of 29 months (95% CI 5.8-4.2); median response time 12 months (95% CI 0.2-11.8). Fishers exact test comparing study sample with P3 cohort showed statistically significant differences in objective response (ORR) vs. 66/147 (45%) ORR vs. 0.05). Conclusions: Outcomes with PA in HR+ EV treated MBCP were worse when compared to the P3 cohort data. Treatment with PA 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.

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-170-glucuronic acid (Exel7-DhExe). UGT2B17*2/*2null genotype is 7 times more common in Asian than Caucasian and leads to reduced Exe glucuronidation in vivo. 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. UGT2B17 genotype was correlated with day 29 Exe plasma active index (PAI) [Table 1] was higher in patients with UGT2B17*6/*6 vs other genotypes (Table 1). 17DhExe Cmax 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 baseline (BL)) was 22%. Exe plasma active index (Exe PAI) (Table 1) was higher in patients with a fall in 17DhExe 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.

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- 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 HR+/HER2- MBC treatment, potentially applicable worldwide. Aim of the present analysis is to verify the adherence to ABC recommendations for HR+/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- MBC pts receiving at least one Chemotherapy (CHT) (SABCS 2016, P5-15-07 & P5-14-09). 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 52.5 years; pN: UK 64 (9.8%), N+=405 (62.2%); Adj CHT=397 (61%), mean DFI=56.9 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 more than 60% of cases in the metastatic setting, 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. Pacifica 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.
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 superioriity 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 subset 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 estimated HR for progression or death at the primary endpoint 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 pooled data incorporating the information from the 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.

1061 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, Universitätsklinikum 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 1078 patients followed up until disease progression for their progression-free survival (PFS) event. We conducted a two-stage process based on a Cox regression model and a stepwise procedure 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. 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 10mg EVE. Patients starting with 10mg showed a significant impact on the PFS (neither as main effect nor within interactions, p-value: 0.44-0.88). Conclusions: Even though the approved and recommeded 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.

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Combination of paclitaxel and LAB43-lg (IMP321), a novel MHC class II agonist, as a first-line chemoinmunotherapy 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. Duboux, Department of Medical Oncology, King’s College London 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 LAB43-lg 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/m²); D1, DB, 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 immune-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 Cmax 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 II dose which is used in the ongoing placebo controlled phase II part of the study. Clinical trial information: NCT02614833.

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: Theophyllinidinositol 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 I study. Methods: Pts with advanced HR+, HER2- breast cancer refractory to standard treatment received LY 200 mg BID and F 250 mg BID (day 1) or 500 mg BID (day 2). Eligible pts had measurable disease and baseline tumor tissue available. 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 asthenia (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 complete response according to RECIST (still on treatment for ≥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.

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 (LLQ) = 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 LLQ (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 LLQ, decreased but not to LLQ, stayed the same, or increased from baseline (cumulative logistic regression). Results: 397 patients with Exe and Let concentration measurements were evaluable (Exe n = 199, Let n = 198). Thirty (7.6%) patients had E2 concentrations above LLQ. Among all patients, E2 concentrations increased 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.
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 postmenopausal 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), while 13 patients met its primary PFS 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-progressing maintenance patients with HR-ABC, who achieved disease control 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+/-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+/-HER2 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/active AE prevention therapies. Insights into real-world dosing and sequence will be presented. Clinical trial information: NCT02753696.

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WG Consensus Statements will be presented in detail. Conclusions: capture grade and timing of toxicity and PROs is warranted. An overview of regardless of line of therapy; PFS is preferred in settings where expected PPS mendations on the appropriate choice of OS or PFS are sensitive to expected consensus on definitions relevant to contemporary CT endpoints. WG recom-

Other effective agents, PROs and toxicity burden. As unique subtypes (e.g. design for MBC should be sensitive to natural history (PPS), availability of industry perspectives, big data and real world evidence (RWE), and patient endpoints by subtype (HR+/HER2-, HR+/HER+, HR-/HER2-, HR-/HER2+) results than those

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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: Tropoeblast 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 TNBC. 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, METABRIC (n=11923) & 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) and 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, trop2e 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+ or intrinsic subtype; in METABRIC & TCGA trop2e was lower in HER2+ than subtypes. In I-SPY 1, trop2e did not vary by hormone receptor (HR) & HER2 all 3 datasets, trop2 was detectable and had a wide range of expression in all BC genes, which may contribute to tumor growth. These findings support the use of trop 2 directed ADC in all BC subtypes.

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Methods: Relevant targeted gene polymorphisms were analyzed by blood in 203 prospective patients (mean age 55.3, median follow-up 24 months). VEGFA at positions -2578C > A (rs9992937), -1487T > 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), CYPC2B1 193C > T (rs1572080), 399T > C (rs10509861) and ABCB1 at positions 1199 C > T (rs2299109), 2677G > TAC (rs2035282) 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-1489T allele was significantly associated with both longer overall survival (OS) (p = 0.006) and DFS (p = 0.065). The VEGFA -2578C allele was associated with greater OS (p = 0.002) and DFS (p = 0.071). These two VEGFA polymorphisms were in linkage disequilibrium (p < 0.0001). Multivariate Cox analysis showed that VEGFA -2578C (p = 0.001) and VEGFR2 1416T (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 58-72) and 89% for score 2 (95%CI 69-96). Conclusion: 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 personalized Beva therapy may serve to be prospectively validated in BC pts. Clinical trial information: 2012-A00244-39.

Methods: An analysis of the UCBG trial COMET—A French multicentric prospective study from R&D UNICANCER. Methods: We retrospectively identified 107 patients with breast cancer (BM) from 2001 and 2012 at 8 institutions. We collected 191 samples which included 28 BM tumor samples (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 tumours was significantly lower as compared to primary tumours. The expression of immune related molecules on tumor cells was converted in BM tumors.

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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 chemotherapeutic 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 800 mg/m2, G 300 mg with PGF administered on day 8 of the cycle. If pt continued on study and there 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 mo), 3 PR, 6 SD, and 3 PD, 4 pts were evaluable for response. **Conclusions:** These data suggest that M+C+G is safe and tolerable, and the most common DLT is neutropenia. This study was as an important step toward 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.

**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 tumorigenesis. 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:** Methods: CIM (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 primary MBC and metastatic (due to blood) randomized clinical trials. **Results:** 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). A nested in a randomized clinical trial of first line chemotherapy (MBC) and 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 meta-analysis on 1944 patients, a CTC count > 5.75 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 first line chemotherapy (MBC), we evaluated the prognostic role of IGF1R expression in CTCs and in circulating tumor cells (CTCs and cell free DNA). 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.
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/m² did not suffer worse cardiotoxicity.

Conclusions: Our study suggests that TP arm is an effective therapeutic alternative for 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.

<table>
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<th>Toxicity</th>
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<th>TE (n=116)</th>
<th>p value*</th>
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*Grade 3 is defined as a toxicity that occurs in <10% of patients. ** p ≤ 0.05.
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 biopsy 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 orthogonal (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: NCT02659832.

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. Archived 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 diagnosis was 9 months. TFx was highly correlated independent of metastatic line of therapy, age at metastatic diagnosis, BRCA status, and primary stage: adjusted hazard ratio between 4th and 1st quartiles = 4.29 (95% CI 1.66-11.1; p=0.0086).

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-naïve 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 RNA sequencing, DNA 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 time points (e.g. initial diagnosis, initial trial recruitment, following completion, etc.) spanning up to 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 transcritps 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 (GREAT) was significantly predicted at 100% and an average of 270 mutations per patient were introduced. PARADIGM integrated pathway analysis shows differential activity in the MYC/MAK 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: Houssaini Tahal 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% HS 1-9%, and 57.75% HS ≥10%. Race was 43.75% Black, and 54% White. Disease stages were 84.4% early (I-IIIA) and 15.6% 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 <1% was significantly higher than ≥10% (HR 0.07-0.32), while mortality between HS 1-9% and ≥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 equally prognostic to ≥10% expression. This study also suggested that chemotherapy. Whether other factors as lympho-vascular invasion, grade, and other parameters change the behavior of the 1-9% HS group remain to be explored.
Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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/RAF 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 MEI1p (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. Mutations in targetable genes co-altered with 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.

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 AA and Ghanaian patients. 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 markers has not been determined. Methods: We aimed 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 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.
Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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. 300 patients will be enrolled in North America, Europe, Israel, and Australia. Patients are receiving C (1000 mg/m2 PO BID for 1.4 days of a 21-day cycle) and Tz (6 mg/kg IV 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.

TPS1108 Poster Session (Board #99a), 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 (monachHER). 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: monachHER 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 mets that are untreated, symptomatic or requiring steroids. Pts are randomized 1:1:1 to Arm A (abemaciclib [150mg PO Q12H] plus trastuzumab Tz [IV infusion 3 weeks plus fulvestrant (F) M (Day 1, 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 measurable (measurable (≥10mm)) disease. 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-CTILILY (1-877-285-4559) Clinical trial information: NCT02675231.

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 have havederegulated phosphatidylinositol 3-kinase (PI3K)/akt/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 clinical activity in pts with estrogen receptor-positive, HER2- advanced BC (ABC) with PI3KCA-altered tumors. SOLAR-1 (NCT02437318) aims to assess the efficacy of ALP + FUL in PI3KCA-mutant and non-mutant tumors in HR+, HER2- ABC setting. Methods: SOLAR-1 is an open-label, single-arm, Phase 1b study conducted in men and postmenopausal women with HR+, HER2- ABC. Pts are randomly assigned (1:1) 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 PI3KCA-mutant cohort. Other secondary endpoints are PFS and OS in the PI3KCA non-mutant cohort, the association between PFS and baseline PIK3CA G84E 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

- Locally advanced or metastatic HR+, HER2- BC
- Recurrence or progression on or after Al therapy
- Identified PIK3CA mutational status
- ≥1 measurable lesion (RECIST v1.1)
- ECOG-PS ≤1
- Ineligibility for ET due to symptomatic visceral disease or other disease of the Lung
- Prior tx with FUL, chemotherapy (except (neo) adjuvant), or PI3K/ AKT/mTOR inhibitors

Exclusion criteria

- Prior ET due to symptomatic visceral disease or other disease of the Lung
- Ineligibility for ET due to symptomatic visceral disease or other disease of the Lung
- Prior tx with FUL, chemotherapy (except (neo) adjuvant), or PI3K/ AKT/mTOR inhibitors
- Premenopausal status

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 unsectable 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 CDK4/6i 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 ESRI 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.

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 HER2-+HR+ tumour up to 50% of the patients receive chemotherapy. Palbociclib (P) a CDK4/6i 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 randomized 1:1 to receive either P or 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 to time to event endpoints; investigator assessed overall clinical response; toxicity and compliance; patient well-being and health care utilization by daily monitoring of treatment impact. Aim: 360 patients will be accrued to show an improved TTF for P in combination with ET. Recruitment will start in Q1/2017 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.

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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.

Methods: HER3 expression in tumor tissue will be evaluated with immunohistochemistry. Efficacy and safety of the RP2D are further evaluated 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, or 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 Escalation 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: NCT02893491.

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-estrogens therapies such as fulvestrant but response durations are often short. Preclinical and clinical studies suggest that simultaneous inhibition of ER and PI3K/AKT/mTOR could predictably delay the emergence of hormone-independent disease 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 2 cohorts: (1) TAK-228 (30 mg) plus fulvestrant (per label), vs fulvestrant alone. Pts will receive 42 days of study drug in each cycle (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 within 12 mos after discontinuation of adjuvant therapy or ≤12 mos after discontinuation in the metastatic setting) and adequate organ function, but not prior therapy with mTOR inhibitors. Efficacy endpoints are investigator-assessed objective response rate and progression-free survival. 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: NCT02950048.
Breast Cancer—Metastatic

**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: Debby 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 0.987; 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 (TN); ≥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 unaltered or only decreased or changing for ≤7 days prior to randomization. **Primary endpoint** is OS. **Key secondary endpoints:** ORR and PFS by RECIST v1.1 and AOs. 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 a 1:1 ratio and 280 pts will be followed (80% power). **Statistical analyses:** **ORR** (≥CR) and **PFS** at 6 months and OS at 1 year, with **QoL**. Pts are monitored for ≥1 year, with ≥2 years follow-up. **Results:** Pts are enrolled through 2023. The IDMC met in Oct 2016 and recommended the study continue unless the treatment effect is not clinically meaningful or does not show futility. To date 38 patients have been recruited from 10 centers. **Conclusions:** Continued enrollment is recommended to evaluate the efficacy and safety of EP vs TPC, with an emphasis on OS, QoL, and progression-free survival.

**TPS1121** Poster Session (Board #105b), Sun, 8:00 AM-11:30 AM

**An open label, phase II trial of continuous low-irradiance photodynamic therapy (CLIPIT) 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 (CLIPIT) 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 CLIPIT 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 CLIPIT with verteporfin in 15 pts with cutaneous lesions from mBC. Pts will receive a single IV injection of verteporfin on day 1. The 9x0cm patch with an adhesive border is placed over the treatment site and attached to the CLIPIT portable pump pack. The pt turns the device on and is monitored periodically for adverse events or response. **Results:** Treatment was well-tolerated with a good response rate and low toxicity. At 8 weeks treatment was stopped in 3 pts due to progression and 2 pts due to skin toxicity. 3 pts have completed treatment up to 3 weeks. 1 pt demonstrated marked improvement in tumor size, and quality of life (FACT-B, a Participant Symptom Scale, and Brief Pain Inventory). Pts derive clinical benefit may be retained 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 CLIPIT. **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.

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Breast Cancer—Metastatic

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 improved 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 metastatic breast cancer is encouraged. Patients will receive pembrolizumab 200 mg IV on day 1 plus nab-paclitaxel 100 mg/m² 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 (ORR) (RECIST 1.1). Secondary objectives include safety, progression-free survival, overall survival, and duration of response. Safety is assessed by a FACs based assay of antigen specific CD3+CD8+ T lymphocyte response and IFN-γ. Secondary objectives include safety, progression-free survival, overall survival, and duration of response. Safety is assessed by a FACs based assay of antigen specific CD3+CD8+ T lymphocyte response and IFN-γ.

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 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 (MEDI4736), 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 mUc4), which is over-expressed in TNBC (Kwa, New York University Cancer Institute, New York, NY). The initial safety run-in with 12 subjects has been completed with no unexpected toxicity. Clinical trial information: NCT02752685.

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 ATP domain 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 (ORR), 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.

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<th>Dose</th>
<th>Paclitaxel (mg/m² IV on days 1, 8, 15)</th>
<th>Onalespib (mg/m² IV on days 1, 8, 15)</th>
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</table>

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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 AlOubayan, 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/HPS 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 2713 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 (5.7%; OR = 2.1; P = 0.044), and a trend for enrichment of PALB2 mutations (3.0%; OR = 2.8; P = 0.056). Secondary analysis of actionable germline mutations in a highly penetrant cancer risk gene set (ATM, BRC1, BRIPI, 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 penetrable genes where cancer screening recommendations for patients and families do exist, are not captured with current testing recommendations.

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 (HRD). The prevalence of HRDef among all tumors is unknown. Methods: Molecular profiles of 48,733 tumors obtained from pts with bladder, breast, ovarian, gastric/esophageal (GE), head/neck, renal, non-small cell lung (NSCLC), pancreatic, sarcoma, and pancreatic neuroendocrine cancers were captured with current testing recommendations. Results: Frequencies of HR gene mutations are depicted in Table 1. Conclusions: The prevalence of HRD among all tumors is 1.61% (5658/34733). Cancer lines 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%, 39/867) & pancreas (5.05%, 102/2022). Frequencies of HR gene mutations are depicted in Table 1. Conclusions: HR mutations were seen in 11.6% of tumors. While the percentage of HRdef in pancreatic cancer patients 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 platinum, but especially PARP inhibitors and newer agents such as ATRX inhibitors.

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 evaluated genetic counseling referrals (GCR) and subsequent GT rates. Methods: All women EC between tightest 2012 and 2015 were identified. Statistical analyses were performed to evaluate risk factors including age, body mass index (BMI), positive family history defined as 2 or more 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 < 0.001) 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 GCR women, 8 (11%) were found to have a mutation on one of the MMR genes. Table 1 lists GCR, GT and positive germline mutations among specific high-risk cohorts. Of these, 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 of cancer have been missed. 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 low 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.

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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 Pennern School of Medicine, Philadelphia, PA

Methods: The COGENT study was a randomized study of in-person (IPD) versus telephone disclosure (TD) of genetic test results. Participants were randomized to receive test disclosure either in person or by telephone. The primary outcome was the proportion of patients who returned for clinical follow-up with a provider for genetic counseling.

Results: Of 195 patients in the IPD arm, 195 (50%) returned for clinical follow-up with a physician to discuss medical management. Among TD patients, 194 (50%) returned for clinical follow-up with a telephone to receive genetic counseling. The study was terminated early due to a large amount of interest in the study. The main reason for non-return was lack of interest in genetic counseling. The study was terminated early due to a large amount of interest in the study. The main reason for non-return was lack of interest in genetic counseling. The study was terminated early due to a large amount of interest in the study. The main reason for non-return was lack of interest in genetic counseling. The study was terminated early due to a large amount of interest in the study. The main reason for non-return was lack of interest in genetic counseling.
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 lifetime 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 occurred in women undergoing mammography screening alone. 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.

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 is 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 2015 to December 2017, 10,000 HRHPV-negative women were enrolled into the cohort and are being followed up every 6 months. We used SPF20/LipA1o 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 infection. 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 HRHPV2015. 10.4% increased 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.

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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 malignancies who underwent evaluation and 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 (4.2%), and colon-endothorium (4.2%). 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 duration mean 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). 1004/1191 (42.3%) had undergone 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. 29.3%; 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 primary cancers. 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.
Knowledge and understanding of genetic test results in men undergoing multigene testing for inherited prostate cancer. First Author: Veda N. Gin, 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 risks 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 regression. 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 regression.

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 = 0.001). Among men with a family history of PCA, 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 = 0.001). Among men with a family history of PCA, understanding GT results vs. actual results.

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.

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 vignette reports, 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 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.

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DNAmAge was strongly correlated with chronologic age ($r = 0.88, p < 0.001$). Tumors were estrogen receptor-positive. Overall, DNA methylation tissue age significantly accelerated DNAmAge as compared to healthy peers ($p < 0.049$). 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.

Baseline screening and psychosocial results from the UK SIGNIFY study: A multicenter prospective clinical trial of patients undergoing intensive screening, including whole-body MRI. There are no published data on the psychological impact of such screening. 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 at 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.

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 ≥ 50 years with and without breast cancer. 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, weight, height, 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 ≥50 with BC = 15, age < 50 without BC = 9). Age range was 24-85 years and 18-85 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.

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 use 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 patients during the study (HR=0.60, p=0.06), with no significant interaction of A/N use and PIK3CA mutation (p=0.34). Conclusions: Among HR+ breast cancer patients, those who used A/Ns following primary diagnosis had longer TTR than nonsmokers, regardless of tumor PIK3CA mutation status. The study provides a model for how tumor genomics could be integrated into secondary chemoprevention studies.
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 56 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: 26767237). 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); HRAS (1); KLF5 (1); MLL3 (1); NF1 (3); PDK1 (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 NVF 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.C668X), CDKN2A (p.Q101W), EGFR (p.T790M) and SMARCA4 (p.S335F/H250S) 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.

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 in 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 BC/OC-affected families and 10,487 control cases with familial BC and/or OC were included in the GC-HBOC cohort for which genetic 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 current study. 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.
Pathogenic gene mutations in emerging cancer genes: What happens after panel testing?

**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 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, FPD5=2) were found in 23% (many of whom lacked family history; typical of these syndromes) whereas 77% had mutations in less well-characterized genes. **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 large number of reported VUS as well as a single academic center; this is 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)**

<table>
<thead>
<tr>
<th>Any risk-reducing intervention recommended (change in screening, preventive surgery, chemoprevention)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in screening recommended</td>
<td>48 (84%)</td>
</tr>
<tr>
<td>Preventive surgery recommended</td>
<td>46 (81%)</td>
</tr>
<tr>
<td>Chemoprevention recommended</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Patient adhered to recommendations</td>
<td>45 (79%)</td>
</tr>
<tr>
<td>Patient shared genetic results with ≥1 relative</td>
<td>52 (91%)</td>
</tr>
<tr>
<td>≥1 relative had genetic testing based on patient's results</td>
<td>36 (63%)</td>
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Germline mutations of PALB2 gene in a sequential series of Chinese patients with breast cancer.

**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 breaks. Germline loss-of-function mutations in PALB2 lead to increased breast cancer risk. Since the germline mutation frequency of PALB2 is much less than that of 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 breast cancer patients. **Methods:** Among the 2279 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 pathogenic variants, PALB2 c.1744C>T, c.3030C>T, 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.3030C>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.

Pathogenicity of mutation analyzer (PathoMAN): A fast automation of germline genomic variant curation in clinical sequencing.

**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, EACX, 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 (PLP), 1272 benign/likely benign (BLB) and 1261 variants of uncertain significance (VUS). **Results:** We report the summary of PathoMAN classifications in four categories contrasted against the manual curation. **Conclusions:** PathoMAN achieves an average of 75% concordance and 1.5% discordance for PLP mutations and 60% and 0.1% for BLB variants. PathoMAN is able to resolve 12% rate and a higher rate of reported VUS as either PLP or BLB. It loses resolution to classify 25% of PLP and BLB 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.

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**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 that of 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 breast cancer patients. **Methods:** Among the 2279 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 pathogenic variants, PALB2 c.1744C>T, c.3030C>T, 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 newly found in this study, among which the PALB2 c.3030C>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.

Clinical implementation of whole genome multi-omics analyses for patients with refractory cancers.

**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%). Pre-panning was done in dedicated precision cancer genomics clinics. **Results:** 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 HIV-positivity. Cancer predisposition germline findings were observed in 3 patients. Of the 96 patients with actionable findings, 74 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 using a multi-gene 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 (10.6%) 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 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 BC or an elevated risk 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.

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). 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. 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 0.7) of MG knowledge between disclosure groups after V1 and V2. Conclusions: 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. 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 \( CDKN2A \) mutation which may be useful for targeted genetic testing in AJ populations. We have compared \( CDKN2A \) mutation status to other known risk factors in FM and found no significant 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).

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 \( BRCA1/2 \) mutation and genetic screening in this population has largely focused on these high-risk 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-\( BRCA1/2 \) 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 less variation 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.

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 BI and 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 \( CDKN2A \) mutation which may be useful for targeted genetic testing in AJ populations. We have compared \( CDKN2A \) mutation status to other known risk factors in FM and found no significant 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).

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1536 Poster Session (Board #1194), 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 nsSNPs were in NSCLC pts (3/29), 68% were extra-TKD (29/122 variants were nsSNPs), 23% within the TKD (23/122). Results: The most frequently mutated nRTKs in breast were JAK1-3 (47%) pts had ≥1 nRTK lesion (0-8). 52/200 (26%) nsSNPs were predicted-damaging (proSNPs) with in silico analysis among 49 pts (6 breast, 13 colon and 30 NSCLC). proSNPs were found in 14/14 nRTKs with median 3 (1-10). The most frequently mutated nRTKs in breast were SRC/2(2/2 variants) andABL2 (1/5), in colon ABL1 (5/10), JAK3 (2/27) andCDK12 (2/28) and in NSCLC: JAK3 (6/20), BTK (2/26), ABL1 (3/12), JAK2 (3/11), CDK12 (3/9) and JAK3 (3/3). Of 180 nsSNPs with in silico results, 68% were extra-TKD (29/122 variants were nsSNPs), 23% within the TKD (13/62) and 9% in pseudokinase domains of JAK1-3 (10/126). Notably, 8/10 pseudokinase domain nsSNPs were in NSCLC pts (3 JAK1, 2 JAK2 and 3 JAK3). Conclusions: >130% 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 proSNPs affect function and if they are clinically actionable.

1537 Poster Session (Board #1195), 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)(p12;q24) between KANK1 and NTRK3, and provided new insights into molecular mechanisms which might identify a subset of metanephric adenomas. Such findings imply that rearrangement may be of prognostic importance. 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 Hisseption 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.

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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 in situ (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.

Soft palatal melanosis as a predictor for neoplasia in the upper aerodigestive tract. First Author: Kenno 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 1,797 Japanese patients, 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 (21.5%) of the subjects (m/f = 1.0:0; distinct, 6-3%; indistinct, aged older than 50 years, 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 regression analysis including the alcohol and aldehyde dehydrogenase 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 numbers of risk factors out of four easily identifiable and significant factors: age ≥55 years, current/former alcohol drinkers, 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 (2.71–9.31) and 7.80 (2.71–28.1), 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.

Cancer Prevention, Hereditary Genetics, and Epidemiology 73s

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 (17.6 vs. 4.7, 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.
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 lower 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 less likely to present with stage I breast cancer (P < 0.0001). NSDBCs were more likely to present with higher stage breast cancer. Rates of mastectomy and CH were 20% higher in NSDBC whereas SDBC had a moderate 10% higher rate of RRT. These findings suggest that screening mammography decreases the extent of local and systemic treatment for breast cancer.

<table>
<thead>
<tr>
<th>Tumor and treatment characteristics.</th>
<th>SDBC</th>
<th>NSDBC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>7807 (63)</td>
<td>4586 (37)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median age</td>
<td>60</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>1534 (19.7)</td>
<td>349 (7.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>II</td>
<td>4150 (53.2)</td>
<td>1322 (28.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>III</td>
<td>1660 (21.3)</td>
<td>1947 (42.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>IV</td>
<td>451 (5.8)</td>
<td>950 (20.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>27.4</td>
<td>48.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>29.9</td>
<td>49.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Loco-regional RT</td>
<td>72.3</td>
<td>66.7</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions: Women with NSDBC are more likely to present with higher stage breast cancer. Rates of mastectomy and chemotherapy were higher in NSDBC whereas SDBC had a moderate increase in regional radiotherapy. These findings suggest that screening mammography decreases the extent of local and systemic treatment for breast cancer.

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Use of a marketing plan for recruitment to a lung cancer screening study. 

First Author: John R. Gaffin, 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 informed (Table 4) most pertinent 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 motives, resulting in specific newspaper advertisements. Screened trial candidates provided demographic and tobacco use data and indicated how they had heard about the study (bus, friend/family, MD, mail, newspaper, radio, TV, other). No site paid for radio or TV time. We used regression analyses to assess whether newspaper 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 years. 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 newsletter (58.6% vs 53.7, chi-squared p = 0.004). Recruitment was more likely (44.0 vs 34.9%, p < 0.001). It was more likely that newspaper was the driver for screening contact compared with candidates with higher education level (OR 1.05/level), higher age (OR 1.03 / yr) and contact at site M (OR 1.131) (all p < 0.001). Recruitment after eligibility screening was higher when newsletter was the driver for contact on univariable but not multivariable analysis. 

Conclusions: The effectiveness of newspaper advertising in motivating study contact may be improved by the formal use of marketing expertise. Newsprint advertising may improve the likelihood of screening. Impressively the APC I1307K carries an overall increase in 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 characteristics focused on breast cancer screening practices for high-risk women. Data were analyzed using Chi-squared tests. Summarized using descriptive statistics; professional characteristic focuses on breast cancer screening practices for high-risk women. Data were analyzed using Chi-squared tests. Summarized using descriptive statistics; professional characteristic focuses on breast cancer screening practices for high-risk women. 

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 motives, resulting in specific newspaper advertisements. Screened trial candidates provided demographic and tobacco use data and indicated how they had heard about the study (bus, friend/family, MD, mail, newspaper, radio, TV, other). No site paid for radio or TV time. We used regression analyses to assess whether newspaper 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 years. 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 newsletter (58.6% vs 53.7, chi-squared p = 0.004). Recruitment was more likely (44.0 vs 34.9%, p < 0.001). It was more likely that newspaper was the driver for screening contact compared with candidates with higher education level (OR 1.05/level), higher age (OR 1.03 / yr) and contact at site M (OR 1.131) (all p < 0.001). Recruitment after eligibility screening was higher when newsletter was the driver for contact on univariable but not multivariable analysis. 

Conclusions: The effectiveness of newspaper advertising in motivating study contact may be improved by the formal use of marketing expertise. Newsprint advertising may improve the likelihood of screening. Impressively the APC I1307K carries an overall increase in cancer risk.

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 intervention) factorial design. Pre- and post-intervention endometrial practice recommendations for prevention (% KI67+). Body weight and serum markers were measured pre- and post-intervention (estrone, FSH, DHEA-S, SHBG, IGF-1, adiponectin, omentin, insulin, glucose, 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 (-4.8%), and placebo (+0.1%). Endometrial proliferation was not changed. Overall proliferation was 7.1% at baseline (Table). 

Conclusions: Metformin+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, patients needed to stratify risk and test prevention strategies, particularly at the endometrial tissue level. Clinical trial information: NCT01697566.
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. Recall concordance was greatest with PSA and least with MAM. Discordance was greater in older patients. If MDs recalled any shared decision making, agreement increased significantly with the addition of PT age and elements of shared decision making. Clinical trial information: NCT02430948.

Conclusions: In a highly educated, diverse patient population, patients and physicians often disagreed on recalled cancer screening discussions. Dis- cordance was greatest with PSA and least with MAM. Discordance was greater in older patients. If MDs recalled any shared decision making, agreement increased significantly with the addition of PT age and elements of shared decision making. Clinical trial information: NCT02430948.
**Results:** 21 patients, each providing one sample at baseline, week 14 (on 2000 mg biochemistry profiles were determined in human serum samples collected in taken off metformin for the last six weeks of the study (week 20). Global 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 key byproducts of 3-hydroxybutyrate (BHB) metabolism, suggesting a potential role of metformin in these changes. 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.

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**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 risk, and relative risk. Cutoffs for breast cancer were 20 years, 30 years, and 40 years; for ovarian cancer, 20 years and 40 years. 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 6.5-11.8%) by the age of 85-years, whilst the corresponding risk of EOC was 0.6% (95% CI 0.2-2.6%). The SRi for breast cancer was 0.93 (95% CI 0.82-1.04) 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 SRi for EOC was 0.79 (95% CI 0.20-3.17) in the overall cohort and 1.74 (95% CI 0.44-6.96) in non-carriers from BRCA2 families. Conclusions: This is the largest cohort study to date of prospectively ascertained true-negatives with 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.

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**Breast cancer in male veterans: The Veterans Affairs (VA) informatics and computing infrastructure (VINCI) big data analysis.**

**First Author:** Anna 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 in our 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. A Cox regression survival analysis indicated 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.
2002 to December 2013. The PNI score was calculated as 10 x serum consecutive stage I-III breast cancer patients who were treated from January Methods: We retrospectively analyzed 653 consecutive stage I-II 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 mm³). 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 prognostic value of the PNI and CONUT in breast cancer. Results: The malnutrition 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 = 0.010) 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.

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-II 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 mm³). 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 prognostic value of the PNI and CONUT in breast cancer. Results: The malnutrition 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 = 0.010) 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.

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 Desler, Meir Medical Center, Kfar-Saba, Israel

Background: Data suggests that GERD with recurrent reflux and microaspiration 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, 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 (CI) for lung cancer were estimated using conditional logistic regression. Adjustment was performed for smoking. Results: The study population included 19143 lung cancers cases and 74473 matched controls. PPI use was associated with a significantly increased lung cancer risk (adjusted OR 1.7, 95%CI 1.64-1.77, p < 0.001). In a sensitivity analysis we observed similar results. However, in a sensitivity analysis we observed similar results. In a sensitivity analysis we observed similar results. Conclusions: Chronic PPI 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 Medicine, 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) had 30+ pack-year smoking history; 2) are currently smokers or have quit within the past 15 years. We excluded adults who 1) have lung cancer; 2) had not seen a physician in the past year. In the weighted analyses we 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 was 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 13.2%, 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. Households with an 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.

1565 Poster Session (Board #222), Mon, 1:15 PM-4:45 PM
Hormone replacement therapy (HRT) among BRCA1,2 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 sexual desire 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% prevers, 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% prevers, 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% prevers, 28% survivors). According to the survey respondents, only 26% of healthcare providers for the prevers 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.
Breast cancer screening in transgender patients: Findings from the 2014 BRFSS survey.

**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 FtM 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.

Incidence and survival trends of cancers diagnosed in young adults (20-39 years): A population-based study.

**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 (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 hematical 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.
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 recent work, this analysis showed an association between higher fiber intake and higher abundance of 

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.
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 BROCAs 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), BRIPI (3), BRCA2/BARD1 (1), FAM175A (1), FANCN (1), NBN (1), SLX4 (1) and TP53 (1). Three recurrent mutations accounted for 12.4% (9/73) of the total: 3 BRCA1 c.3331_3334delCAAG (known European mutation), 3 FAM175A c.211A > G (known European 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 admixed pattern of the Brazilian population. This result underscores the importance of using multiplex assays in genetic epidemiologic research of understudied populations where unexpected findings, such as the recurrent and novel variant in PALB2 c.1671_1674delTATT, can be detected.

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, controls (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. Data were 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 OR of 2.0, with 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 = 63.9 years), 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 = 0.688). 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 = 0.008, OR = 1.78). Serious life-threatening events within the past year were more noticeably 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.
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 germine, 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 germine genetic testing and include yield of pathogenic germline mutations, discordance between germine 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 germine testing. We identified 52 LP/P germline variants in BRCA2 (17), BRCA1 (7), PALB2 (6), MUTHY (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, germine testing revealed variants that were absent in TMP results and provided new information about inherited cancer risk or familial 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 nor family criteria nor the latest NCCN guidelines for germine testing in patients with TMP. Also striking were nine patients whose germine LP/P mutations were absent in TMP results. These data suggest that indications for germine testing of cancer patients must be expanded to avoid missing important germine findings in patients undergoing TMP.

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 2015, the Supreme Court ruled that isolated DNA sequences could no longer 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). 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 CHEK1 (19), APC (44), MSH6 (51), 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 significantly in the years following the 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.

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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: Junnie 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 pedigree/clinical 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% 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/p16 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 tanned 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 risk of ovarian cancer alone. 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 (3.0%). 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 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.

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. Overall, 14.3% (5,509) of the 42,393 patients we estimate almost 12% of pathogenic variants across these cancers. 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.

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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-squared 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 9%, respectively, while GB tests revealed a PV and VUS at rates of 21% and 18%, respectively. 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 factors contributing to changing trends in genetic 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 multilethnic 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 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 software 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-genic 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 with lower costs for NGS-based testing and growing numbers of actionable targets coupled with targeted therapeutics. Early MGTP 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 with metastatic CA. All PTs/COs completed baseline and follow-up (FU) assessment surveys. COs were shown how to access FACC (access) and tested w/50-100 MGTP. 12% blocks were inadequate. MGTP results were presented when appropriate at FACC’s Genomic Tumor Board. All MGTP yielded ≥1 variant (Var) (range 1-6). 13/22 (59%) pts tested had a clinically relevant Var; 6 other Vars were potentially actionable w/ approved therapy, while 3 Vars have novel therapies in Phase I/II studies. MGTPs 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 therapeutics (67%). At FU, 4/8 (50%) COs found GC “very useful”, and 6/3 reported MGTP paired w/GC would “probably/definitely” increase rate of MGTP use. Most (88%) felt MGTPs should be offered to PTs w/uncurable 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 MGTP-targeted experimental therapy. At FU (n = 14), 86% felt MGTP was valuable, yet only 46% would “definitely” retest, and only 31% would pay $100 to retest, even for 50/6 genes. Conclusions: GC can be effective in 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.
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 were 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.

TP51591 Poster Session (Board #248a), 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 Baillenger, Indiana University, Indianapolis, IN

Background: Obesity represents a challenging epidemic associated with increased risk of several malignancies, including breast cancer in post-menopausal 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 is a 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.

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Central Nervous System Tumors

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 and 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-CSF), 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 19 PPV patients (4.1, 1.2-8.0 months) 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 Center 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反映了ection 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 × 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 ≥30% necrosis/reactive changes and ≤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 = 11), 15 had potential treatment-related effects and 8 had effects consistent with progression. Of the 20 patients treated with nivo 3, 7 were reported by the treating physician as immune-related, then treated with nivo 3 + ipi 1, and 12 were continued with nivo 3. Of the 11 patients treated with nivo 3 + ipi 1, 3 were reported by the treating physician as immune-related, then treated with nivo 3, and 8 were continued with nivo 3 + ipi 1. Conclusions: These results suggest that histopathologic analyses may help better inform decisions on continuing nivo ± ipi in challenging cases, and show that immunotherapy may have intracerebral biological activity. Clinical trial information: NCT02171771.

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 were randomized to receive a single intratumoral injection of 3E10 vp DNX-2401. Patients were randomized in a 2:1 ratio to receive 50 mcg/m2 of subcutaneous IFN (Actimmune) QW initiated 14 days after DNX-2401 or to be followed with IFN QW initiated 14 days after DNX-2401. 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, though IFN therapy was stopped early. However, OS of IFN group 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 ≤ 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 trial 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 are pooled for analysis. Eligible adults had GBM, centrally confirmed EGFR amp, and KPS ≥ 70. Pts received 0.5-1.25 mg/kg ABT-414 on days 1 and 15 +/- 150-200 mg/m2 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, ≥ 25% pts) were ocular (90%) and included blurred vision (84%) and photophobia (31%), which were mainly reversible. Common non-ocular AEs were fatigue (36%) and headache (30%). Grade 3/4 AEs (≥ 5% pts) included ocular toxicities (29%) and decreased platelets/thrombocytopenia (10%). Serious AEs included seizure and keratitis (2% each). Of 126 pts evaluable by RANO, 52% had improvement or stabilization (OS, 15%); and OS 18-24 (0.9%) patients died. Of 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-segregation 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 tolerably low, and results from ongoing randomized trial of ABT-414 vs. ABT-414 + TMZ vs. TMZ/omustine in EGFR amp, rGBM has completed accrual with results expected later this year (NCT02343406). Clinical trial information: NCT01800695.

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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. Pleomorphic 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 gliomas) 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 responses lasting 16.8 months 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 AE was headache (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 1, 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 5d/28d cycle. Each arm had standard 3+3 design. A combination cohort with both concurrent and adjuvant AZD1775 at MT and analysis of PK/PD and IDD at MT 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. 527 mg one patient had grade 3 fatigue and another had grade 4 thrombocytopenia and neutropenia. Two of 6 patients had grade 3 low neutrophils lasting 12.9 months and 14 months (grade 3). 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 (38%). Enrollment in the combination cohort was completed and evaluation of safety is underway. The drug concentration in contrast enhancing and non-enhancing brain tumor was 4.8 x 10^{-6} greater than plasma, respectively for patients on IDD portion. Conclusions: The MTD for AZD1775 in combination with concurrent RT/TMZ and 425 mg qd 5d/28d cycle in combination with adjuvant TMZ, IDK 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-naive, 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 for AZD3759, 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 the TKI-naive and TKI pre-treated cohorts of the phase II BLOOM trial (NCT02283869). 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 phase (PE). Patients with BM/leptomeningeal metastases (LM/LM) pre-blind treated with EGFR with ESCC were recruited into the expansion cohorts of this study: 16 patients with TKI naive BM and 4 patients with TKI naive 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 Cmin, free plasma and CSF exposure at both doses were above pEGFR IC50. By investigators’ assessment, the intracranial objective response rate (ORR) was 63% (12 out of 19 evaluable patients) and 19% (3 out of 16 evaluable patients) confirmed/unconfirmed partial/complete response (PR/CRI), 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 sustained inhibition and demonstrated promising anti-tumor efficacy in both intracranial and extracranial tumors in TKI-naive patients with CNS metastasis. Updated clinical data will be shared at the meeting. Clinical trial information: NCT02283869.

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 Bonnetete, 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 GENEMO study (NCT00959566). 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. In 2016, 384 blood samples with PI3k-Akt-mTOR polymorphism (coding and non-coding) and non-CNS metastatic patients (no neurological symptoms or normal brain MRI before death or during 5-years metastatic period) were selected. 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), PI3KRI (11), PI3KCA (20), PTEN (17), RPS6KB1 (6). Results: Of the 342 patients with metastases in the GENEMO 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, genes with SNPs significant associated with CNS metastasis were AKT1 rs3803304, AA of AKT2 n3730050, CC of AKT2 rs8100188, TT of PDK1 rs1168690, GG of PDK1 rs11904366 and GG of PI3KRI rs251408 were associated with CNS metastasis at the p < 0.05 threshold. Only gene copy of PI3KRI rs706716 was statistically associated with CNS metastasis after Bonferroni correction (p = 0.0003, < 0.00085). Conclusions: PI3KRI-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.

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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 1/2 pre-operative 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 (range 120-1129) were 30.4ng/g in the 2Gy arm and 40.2 ng/g in the 4Gy arm. A dose-dependent increase was seen for both 2Gy and 4Gy arms. Afatinib concentrations in resected tumour were dose dependent and ranged from 1.5 to 20.1 cm$^3$. Conclusions: This was a phase 1b trial investigating the safe and effective delivery of afatinib with low-dose RT. Median afatinib concentrations in resected tumour were dose dependent and ranged from 1.5 to 20.1 cm$^3$. Conclusion: CamBMT1 is a phase Ib/2 pre-operative window-of-opportunity trial designed to test if the delivery of afatinib into brain mets might be enhanced by targeted, low dose-RT. 2008 Oral Abstract Session, Sun, 8:00 AM-11:00 AM 2008 Clinical Science Symposium, Sat, 3:00 PM-4:30 PM
Phase II trial of bevacizumab and temozolomide for upfront treatment of elderly patients with newly diagnosed glioblastoma. First Author: Phaninh Lea Nghiemphu, University of California, 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 radiotherapy.

Methods: This is a phase II trial of newly diagnosed GBM patients aged 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/m² for 5 days out of 28 days, up to 12 cycles) until tumor progression. Primary outcome measures are overall survival and safety evaluations.

Results: First June 2016, 50 GBM patients enrolled in this study. To date, all patients have tumor progression and 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 had 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), but detected no prognostic role for T2, ADC or FET signal intensity.

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.

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 comparison with intravenous BEV 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/N20 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 PET 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: Sourav 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. Volume metrics 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 109 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.
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 DCE and DSC 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 VDI. 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).

Identification of novel therapeutic targets in glioblastoma with functional genomic mRNA profiling. First Author: Cynilo 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 unregulated genes in GBM with known antineoplastic drug interactions. Methods: Publicly available, raw microarray expression data of patient-derived GBM samples and normal 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 EGRF 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 to clinical research is needed to investigate in vivo inhibition of these druggable genes is necessary and may lead to an improvement of treatment outcomes for patients with GBM.

Low grade glioma patients with IDH mutation and 1p19q codel: To treat or not to treat? First Author: Ennio 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 codel (codeleted) 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. 1p19q 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 RT0G 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 FFS (mFFS) was 59.6 months (95%CI: 41.8-77.4) and was significantly longer in pts who received surgery and postsurgical treatments (79.5 months, 95%CI: 60.5-65.6). mOS of pts who received FU (46.3 months, 95%CI: 36.0-56.5; P=0.001) mFFS 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 FFS. Conclusions: Our study evaluated the role of treatments in LGG pts assessed with NGS and FISH. Post-surgical treatments are crucial to extend progression-free survival 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.

RNA-Seq analysis of glioma tumors to reveal targetable gene fusions. First Author: Deepa 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 fusions with preserved kinase domains were investigated. Results: Among 404 gliomas tested, 39 (9.7%) presented potentially targetable fusions, of which 24/256 (11%) of glioblastoma (GBM), 5/42 (12%) of anaplastic astrocytoma (AA), 2/25 (8%) of grade III astrocytoma, 1/4 (25%) of grade III astrocytoma with preservation of the kinase domain (AKA), 1/5 (20%) of astrocytoma (PA) harbored targetable fusions. In GBMs, 1 of 15 (6.7%) IDH-mutated tumors had a fusion with a kinase (2 of 17.5%) IDH-wild type tumors had fusions. 46 oligodendrogial tumors were profiled and no fusions were seen, which was lower than frequency of fusions in astrocytic tumors (34/304, 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-BRAF (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; including NTRK1 (BCAN-NTRK1, PA); 6 NTRK2 (1 NOS1AP-NTRK2 in AA; DRK4 in GBM; NTRK2, KDCT8-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). FGFR fusions (2 EGFR-SEPT14 and 1 EGFR-VWC2) were seen in 3 GBMs, BRAF in 3 (1 KIAA1549-BRAF, 1 LOC1000053631-BRAF in PA and 1 ZSCAN23-BRAF in glioma NOS) and PDGFRα (RAB3I-PDGFRα) in GBM in 1. C11orf95-REL A fusions were seen in 2 of grade III ependymomas but not in the 2 grade II ependymomas. Conclusions: We report targetable fusions in the group of gliomas involving NTRK, MET, EGFR, FGFR, BRAF and PDGFRα in glioma. Including novel fusions that haven’t been previously described in gliomas (e.g., EGFR-WC2, FGFR3-NBR1). Fusions were seen in over 10% of astrocytic tumors, while none was seen in oligodendroglias. Identification of such kinase-associated fusion transcripts may allow us to exploit therapeutic opportunities with targeted therapies in gliomas.
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 Chien-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 (NCT0228369), 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 un-selected 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 6.0 mo; 21 pts ongoing. Clinical trial information: NCT01390571.

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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 Maruthi Pali, 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 temolozomide 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 alternate 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. Consensus of Cohen's kappa coefficient. Results: 112 patients were screened and 65 were accrued. All patients underwent both VF and CF. The concurrence in decision of administering temozolomide between VF and CF was 100% (Cohen kappa = 1.0, 95% CI 1.0-1.0, p < 0.00), in case of medication decision (k = 0.66, 95% CI 0.45-0.87, p = 0.00), imaging decision (k = 1.0, 95% CI 1.0-1.0, p < 0.00), rehabilitation decision (k = 1.0, 95% CI 1.0-1.0, p < 0.00) and molecular testing decision (k = 0.65, 95% CI 0.20-1.0, p < 0.00), the agreement was substantial. The satisfaction rate was 100% post video follow up and was 96.5% post clinical follow up. The median cost incurred in VF was 58.15 USD (IQR 43.38-91.69) while that incurred in CF was 151.23 USD (IQR 88.2-256 (p < 0.00)).

Conclusions: The decisions taken regarding administration of adjuvant TMZ were similar between VF and CF. Hence, it's practical and economical to substitute CF with VF during adjuvant TMZ administration. Clinical trial information: CTRI/2017/01/007626.

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 oligodendrogliomomas: An AINO (Italian Association for Neuro-Oncology) study. First Author: Roberto Ruda, Department of Neuro-Oncology, University of Turin and City of Health and Sciences, 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 oligodendrogliomas was performed. Inclusion criteria were as follows: 1) age > 18 years; 2) proven grade II oligodendroglioma or oligocystrocytoma; 3) 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, time to progression after surgery and OS. Results: Of 28 patients, median age was 59 years (18-65), KPS > 80 in 19 patients, 14/60 (23%) had EFU, 21/60 (35%) and PD in 4/60 (7%). 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 15 (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 1/149 (22.4%) were IDH 1-2 wild-type with a PFS of 45.8% at 6 months and 25% at 60 months with a median value of 34 months. OS was 96% 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 TMZ (3 vs 6 months). Conclusions: Dose-dense TMZ has the potential to alter the natural history of recurrent grade II gliomas. In particular, we have shown that IDH1-2 mutated/1p19q codeleted patients are more likely to be seizure free and have a longer survival. Clinical trial information: 2007-00386-38.

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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%) patients 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.

Results: Statistical similarity (p = 0.919) for CA and CRT at 5 years (69.1% vs. 68.5%), 6cm, astrocytoma histology, and older age were predictors for worse survival. Type was not a significant predictor for OS (p = 0.125), while tumor size at an academic program (65.2% vs. 50.3%). MVA demonstrated treatment deleted (22.8% vs. 7.5%), younger median age (47 vs. 48 years) and treated at an academic hospital in Switzerland, where Bev is registered and reimbursed for rGBM. Methods: Using the National Cancer Data Base (NCDB), high risk (age ≥ 40 or STR) grade II glioma patients with oligodendroglioma, astrocytoma, or mixed tumors were identified. Patients receiving CA were compared to patients receiving CRT. Results: Kaplan Meier statistics were utilized to compare OS and PFS. 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. 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.
Conclusions: More than 50% of high grade glioma patients were included in this retrospective cross-sectional study. Nineteen patients were excluded because of the lack of appropriate pathology slides for pathologic evaluation. 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. Patients were treated by LIPU until tumor progression. In 65 ultrasound passages, two to four minutes of LIPU in combination with the impact of therapies. The aim of this study is to determine if PD-L1 expression status changes in recurrent gliomas after chemoradiotherapy.

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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 < 1x10-5) 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 < 1x10-5). Stratifying MUT by tissue rRS, median OS was 197, 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 codelleted vs non-codelleted 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 differentiate 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.

Overall survival (OS) by line of therapy (LOT) in Medicare-enrolled glioblastoma multiforme (GBM) patients (pts), First Author: Abhalla Aly, Pharmirnet 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 yrs 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 operated (OL), infilt line (1L+) and infilt+sec line (1L2+). OS was estimated by the Kaplan-Meier method from dx for 0L, and from LOT characterized as untreated (0L), biopsy alone (B), tumor size, age, and CCI (Table). Results: Among 2533 eligible GBM pts (median age: 74 yrs; 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 months (mos) with 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.

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.
Conclusion: DUR is a human IgG1 monoclonal Ab against PD-L1. PD-1/PD-1 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) evaluated safety/tolerability 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, C2 = 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] yrs; baseline ECOG PS: 51.6%; PS1: 48.4%; baseline measurable lesions: 77.4%). Incidences of treatment-related adverse events (AEs) by max CTCAE grade (Gr) were Gr1: 53.5%; Gr2: 41.9%; Gr3: 9.7%; and Gr4/5: 0%. Most common AEs (≥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 20%; stable disease, 1 (3.9%) pts; and stable disease, 14 (44.8%) pts. At 1 y, 4 pts remained progression free (longest PFS ongoing at 80 wks, n=2). OS-6 and OS-12 were 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 naive recurrent GBM pts. Study is ongoing. Clinical trial information: NCT02336165.

Expanded phase I study of intratumoral Ad-RTS-hIL-12 plus oral veledimex: Tolerability and survival in recurrent glioblastoma.

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: We used a multicenter Phase I dose escalation trial and expansion cohort to evaluate a treatment regimen with progressive or ongoing Grade III or IV glioma undergoing resection was injected intratumorally with Ad 2 x 10^11 viral particles and daily oral for 15 doses, beginning prior to surgery. The primary endpoint is safety and tolerability of Ad + V; secondary endpoints include OS and PFS.

Results: 25 subjects were enrolled in 3 dose escalation cohorts: 20 mg (n = 7), 30 mg (n = 4), and 40 mg (n = 8) 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 AE's >Grade (G)3 AEs in the 20 mg cohort was significantly lower: 20% in 20mg, 50% in 30mg, and 50% in 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. In 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: NCT02626271.

Assessment of tumor hypoxia in BEV resistant GBM using FMISO PET and MRI. A cohort of 113 GBM 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 elimination and forward inclusion" algorithms to pick up the most effective features with a $p < 0.05$. From 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: Global-Uniformity, AUC: 0.749, standard deviation, AUC: 0.749, and hit count, AUC: 0.749. The predictive performance of the radiomics model was validated to be far more valid than the clinical predictors (indistinct tumor border and heterogeneous signal intensity) with the higher area under curve (AUC). Compared with the best single feature Global Uniformity, 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 high prediction accuracy, providing reliable basis for the pre-operative treatment regime.
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 oral-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 153 days [range: 70-359]), 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). PF6 was 42% in the CBD:THC group and 35% in the placebo group (NS). Overall, the commonest treatment related toxicities were dizziness (in 1/18 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.
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 understanding of glioma heterogeneity is required for improved treatment strategy. First Author: Ina Ly, Massachusetts General Hospital, Boston, MA

**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). Radio graphically 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 (↑24%), 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%).

**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.

B gev (Bev) to reduce the negative impact of glioblastoma (GBM) tumor size on survival from first recurrence. First Author: Huy Tran 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), or both drugs (n = 53). We found OS of Bev group was significantly better 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 (standard 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.

**Conclusions:** To minimize selection bias, we identified another control group among the groups, and high rate of crossover (7%). OS for CCNU 01-04 (mOS = 5.7 mo) was similar to the Bev groups. Across all groups 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.
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: Ofranogene 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 1x10^12 viral particles bimonthly until progression, followed by BEV standard of care (LE cohort). The protocol was amended to allow treatment through progression (TTPH) 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 TTPH 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 TTPH cohorts during the early progression period (local data); median 5% increase per 30d: 14.8 ± 14.1, p = 0.98). In the TTPH cohort, growth was attenuated after the 1st progression, compared to the preceding VB-111 monotherapy period (MPS: 0.6 ± 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 VB-111 progressed GBM. 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 endpoint 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 infection, an EOG 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/m² 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≥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 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 (local data). Of the 7 SD pts, 4 progressed after 4 cycles of treatment and the remaining 3 pts remained 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 neutrophil 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 assessed by American Academy of Neurology criteria. A 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 calculated for each patient, average slopes were compared across therapy groups using the Wilcoxon Rank Sum test. Results: 3, 431 0.69 0.55 0.87 0.001 6 (4-12)
N (participants) NNT (95% CI) P
3 Year Progression, Chemotherapy vs Control
3 431 0.69 0.55 0.87 0.001 6 (4-12)
10 Year Progression, Chemotherapy vs Control
3 431 0.58 0.39 0.77 0.008 3 (2-12)
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 12.5 (8-30)
10 Year Progression Early RT vs Control
4 1114 0.74 0.60 0.91 0.005 3 (1-17)
Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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, CD133, 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 pool had undergone resequencing 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.

Background: A human pilot study for recurrent GBM patients is underway. Blockage of MIF expression, increased apoptosis and longer survival in vivo. Method: 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 ibudilast (MN-166; 3-isobutyryl-2-isopropylpyrazolo-[1,5-a]pyridine) to blockage of 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.
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 supratentorial in 2, cranium outside TB in 1, craniopinal 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 survival 84% and 50% 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 MRT 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.
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 (Vennooij et al. 2007), which accounts for about 36% of all primary intracranial tumors (Ostrow et al. 2018). 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 = 0.2, 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 (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.

Epidemiologic and Genetic Considerations in the Management of Primary Cerebral Metastases. 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 anti-cancer therapy. First Author: Byoung Chul Cho, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

Results: As of September 26, 2016, 38 patients were recruited into the expansion cohorts of this phase I study. Of those, 18 were TKI pre-treated and 10 patients were enrolled with LM. 10 patients were enrolled with LM and plasma were collected from 20 patients with brain tumors and was used to characterize tumor specific mutations. Methods: 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 cDNA in CSF and plasma were collected from 20 patients with brain tumors and was subjected to enrichment for a 1.15M size panel covering > 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 cDNA 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 cDNA of a patient with brain metastasis lung cancer. Conclusions: Cerebrospinal fluid cell free DNA analysis could be a potential alternative analysis for patients with primary or metastatic brain tumors.
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 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< 0.0001). 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; 5-10 lesions, 8.4 months, HR 1.41; > 10 lesions, 6.9 months, HR 1.19, p< 0.0001). 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 vs patients with EGFPR+, HER2+, and ALK- disease who had no difference in survival based on number of metastases, while patients with BRAF V600and 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.

Neurocognitive function testing and health related quality of life in stage IV lung cancer patients with and without brain metastases. First Author: Graine M. O’Kane, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Survival in stage IV lung cancer (SALC) 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 SALC pts with BM status. Methods: SALC pts with BM (≥4+) 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). HRQoL was measured using the EQ5D-3L surveys (Pearson Coefficient, R). Results: BM+ (n = 54) and matched NBM (n = 40) pts had similar demographics. The overall median age was 61 years; 59% were female; 85% that were adenocarcinomas, half had EGFRL858R 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) was 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 HVLT 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, HVLT scores were better in untreated patients (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: Significant NCF impacts HUS in SALC pts and should be considered in treatment planning. HVLT scores are useful to assess specifically the impact of BM and WBRT in SALC pts, and is reflected in associations with HRQoL.

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 hemorrhagic, offer prognostic value in BM from melanoma. This study reports on 4 biomarkers, glio, 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 1989-2015 was created across 4 sites. Glio, immune, and hem (grouped 0-1-3) and nec (0-2 v 3) were scored via H&E stain (0-3). Overall survival (OS) 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 subtypes (n = 158) was 36% HER2+, 26% HER2−; 38% HER2−/TN. Across all samples, expression of glio 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 ± 0.62 (p = 0.03), 1.31 ± 0.93 (p = 0.03), 1.07 ± 0.92 (p = 0.92) respectively. Nec was associated with inferior OS: 0.38 ± 0.10 (p = 0.001). 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 clinicopathologic 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 role of BCBM microenvironment both refines prognostic considerations for this pt population and may lead to future investigations of targeted immunotherapies in select subtypes of BCBM.

Neurocognitive function testing and health related quality of life in stage IV lung cancer patients with and without brain metastases. First Author: Nancy U. Lin, Dana-Farber Cancer Institute, Boston, MA

Background: Survival in stage IV lung cancer (SALC) 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 SALC pts with BM status. Methods: SALC pts with 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 of utility score (HUS) data were analyzed using the EQ5D-3L surveys (Pearson Coefficient, R). Results: BM+ (n = 54) and matched NBM (n = 40) pts had similar demographics. The overall median age was 61 years; 59% were female; 85% that were adenocarcinomas, half had EGFRL858R 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) was 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 HVLT 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, HVLT scores were better in untreated patients (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: Significant NCF impacts HUS in SALC pts and should be considered in treatment planning. HVLT scores are useful to assess specifically the impact of BM and WBRT in SALC pts, and is reflected in associations with HRQoL.

Efficacy within OS per BRAF mut status

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104s Central Nervous System Tumors

**2076 Poster Session (Board #318), Mon, 1:15 PM-4:45 PM**

**Title:** Detection of unknown primary site (BM-CUPS)

**Authors:** 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 18F-fluorodeoxyglucose positron emission tomography (FDG-PET/CT) in the detection of the primary lesion is 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%).

**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**

**Title:** Linac-based radiosurgery for multiple brain metastases: A quality assurance and feasibility study.

**Authors:** Raphael M. Pfetter, 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 (M3M) 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 M3M. System QA included ArchCheck diode array and film dosimetry and gel dosimetry based on a patient derived phantom. Individual QA included replanning 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 per brain metastasis. SRS was delivered using 4-5 (is more 7-10 since return arc 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 of 45 minutes. This is the same as the time for each individual metastasis on earlier planning systems and compares to the planning time and 12 mins delivery time for each of 10 fractions for a conventional 2 field WBRT plan (median 140 mins). 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 radiation oncology departments which will allow more prospective studies of SRS for multiple metastases.

**2078 Poster Session (Board #320), Mon, 1:15 PM-4:45 PM**

**Title:** Outcomes from 735 patients with breast cancer brain metastases (BM) according to biological subtype, number of BMs, and systemic treatment after local therapy.

**Authors:** 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 2003-2019. Whole brain radiotherapy was undertaken in 79%, surgery 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 survival 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 untreated and treated systematically within the TNBC, HER2+ER/PR-, HER2+ER/PR+ and Luminal subtypes corresponding were respectively 6, 10, 14, 11 and 2, 3, 2, 1 months (p < 0.001). Median survivals of 171 patients with a single BM treated and untreated systematically were respectively 15 and 5 months (p < 0.001). Median survivals of 70 patients with solitary BM treated and untreated systematically were respectively 21 and 10 months (p < 0.0001). 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 best 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**

**Title:** Individualized screening trial of innovative glioblastoma therapy (INSIGHT).

**Authors:** 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. INSIGNiT (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:** INSIGNiT 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 and with 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, PI3K/mutation, AKT3 amplification, PIK3CB > 1 copy gain, or PTEN dual loss; CDK: + patients with wild-type Rb1 and CDK4 amplification, CDK6 amplification, or CDKN2A > 1 copy gain, or PIK3CA mutation/amplification, PI3K/mutation, AKT3 amplification, PIK3CB > 1 copy gain, or PTEN dual loss. These randomized 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.
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, metabolic 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 and if 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 (historical 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 = 0.025. The trial is open and enrollment will begin in Feb 2017. Clinical trial information: NCT003032484.

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 human 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 line and xenograft models. Based on MGMT status and drug response, 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/m2/day 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 low response (clinicaltrials.gov identifier: NCT02719762). 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 ≤ 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 in combination with HFSRT to recurrent high grade gliomas. Objectives include analysis of specific angiogenic and metabolic biomarkers in tissue and long-term survival in orthotopic murine models of glioma. This report synthesizes findings from nivolumab as monotherapy (NCT02476095) and in combination with HFSRT (NCT02829931). Results: As of Jan 2017, 105 pts (8 male, 97 female) have been enrolled in the phase I dose expansion cohort. The majority of pts were WHO grade IV glioblastoma (93%). The most common cause of enrollment was recurrent disease (69%), followed by progression on temozolomide therapy (18%) and progression on prior therapy (5%). All pts were evaluable for safety analysis (Additional analyses will be presented at the meeting). Conclusions: The safety and tolerability profile of nivolumab combined with HFSRT in pts with recurrent glioblastoma appears promising. The combination of nivolumab and HFSRT is feasible, and the combination of these two agents appears to provide a tolerable and safe treatment option for patients with recurrent glioblastoma. The preliminary antitumor activity observed with this regimen suggests that this combination treatment may have activity in recurrent glioblastoma.

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 Center and Research Institute, Tampa, FL

Background: Nivolumab and HFSRT have shown activity in recurrent high grade gliomas. This randomized phase I trial evaluated the safety and tolerability of nivolumab combined with HFSRT in pts with recurrent high grade gliomas (WHO grade III or IV). Methods: This phase I trial evaluated the safety and tolerability of nivolumab combined with HFSRT in pts with recurrent high grade gliomas (WHO grade III or IV). The trial included a safety cohort of 6 pts followed by a dose expansion cohort of 20 pts (NCT02829931). Pts with bevacizumab naïve recurrent WHO grade III or IV gliomas (maximum diameter of enhancing brain lesion ≤ 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 in combination with HFSRT to recurrent high grade gliomas. Objectives include analysis of specific angiogenic and metabolic biomarkers in tissue and long-term survival in orthotopic murine models of glioma. This report synthesizes findings from nivolumab as monotherapy (NCT02476095) and in combination with HFSRT (NCT02829931). Results: As of Jan 2017, 105 pts (8 male, 97 female) have been enrolled in the phase I dose expansion cohort. The majority of pts were WHO grade IV glioblastoma (93%). The most common cause of enrollment was recurrent disease (69%), followed by progression on temozolomide therapy (18%) and progression on prior therapy (5%). All pts were evaluable for safety analysis (Additional analyses will be presented at the meeting). Conclusions: The safety and tolerability profile of nivolumab combined with HFSRT in pts with recurrent glioblastoma appears promising. The combination of nivolumab and HFSRT is feasible, and the combination of these two agents appears to provide a tolerable and safe treatment option for patients with recurrent glioblastoma. The preliminary antitumor activity observed with this regimen suggests that this combination treatment may have activity in recurrent glioblastoma.

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 xenographs (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 (α = 0.20, β = 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.

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Debio 1347, an oral FGFR inhibitor: Results from a first-in-human, phase I dose-escalation study in patients with FGFR genotypically 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 non-hematologic (73%), fatigue (41%), diarrhea (39%), nausea (37%), and inaptness (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 h; hyperphosphatemia was dose-dependent. Among the 54 response-evaluable patients, 4 confirmed and 1 unconformed partial responses were observed in patients with cholangiocarcinoma (FGFR2 mutant), uterine (FGFR2 and FGFR1 amplified), colon (FGFR2 mutation), and urothelial cancer (FGFR3 fusion); an additional 10 patients had tumors progression <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.

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.

Centini+ plus nicholinab (NIVO) in patients (pts) with anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer (NSCLC) as a novel phase II study. First Author: Enrique Feliu, 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 PD1-170

Cancer Center, New York, NY

Results: progression/unacceptable toxicity. Primary objective: MTD/recommended with low-fat meal, at 450 mg/day (group 1) or 300 mg/day (group 2) until stage IIIB/IV ALK+ NSCLC; who received NIVO 3 mg/kg IV Q2W + ceritinib previously treated (ALK inhibitor [ALKi] or chemotherapy) or tx-naive pts with ALK+ advanced non-small cell lung cancer (NSCLC). However, the protocol will be amended to address observed toxicities. Data will be updated for presentation. Clinical trial information: NCT02360345.

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: NCT02360345.

An investigator-initiated phase I study of ONX-0801, 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 >20%); no dose limiting toxicity was seen on schedule B. No grade 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-re and 4/4 AFR-re 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.

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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.

**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 selectively oral 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 21 days (1 cycle = 3 weeks; Arm B). Bayesian Logistic Regression Model was used to guide dose escalation. Hhex1M1, 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 (0.25 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 evaluation. 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%), nausea (14%), stomatitis (14%), increased CK (11%), neutropenia (11%) and vomiting (11%). DLTs included: thrombocytopenia grade (G) 4 (n=3), increased troponin G (n=1), hypophosphatemia G3 (n=1), multiple G2 events in 1 pt preventing adequate dose intensity in cycle 2. Of 21 evaluable pts, 3 had partial response (PR); one was confirmed and had stable disease (SD) lasting >4 cycles. One patient had stable disease (SD) lasting >4 cycles. **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.

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**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 patients with advanced 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 xenograft models of Ras and RAF-mutated cancers. We present data from the Ras/Raf/RAF-mutated advanced solid tumor cohort and the initial results for the multiple myeloma (MM) cohort. **Methods:** Patients with KRAS, NRAS or BRAF mutation that failed previous treatments were treated with RO5126766 using a novel 3+3 dose escalation 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. **Results:** Assessment was completed using RECIST 1.1 criteria for solid tumors and ISS criteria and ISS criteria was used for MM. **Results:** A total of 20 patients with solid tumors (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-mutant had received 2 previous lines of MEK inhibitors and the BRAF mutant had previously received a BRAF inhibitor. In the gynaecological group, 4 patients with colorectal cancer (2 BRAF and 2 NRAS), patients with melanoma and 1 patient with melanoma were treated and none responded. Two patients with MM have been treated so far (1 KRAS, 1 KRAS+NRAS). The one evaluable patient had an indWg partial response (PR) after 1 cycle (FLC-x from 324 mg/L to 161 mg/L, ratio 0.03 to 0.08) without concomitant dexamethasone. This patient was previously treated with an immunomodulatory drug, a proteasome inhibitor and two ASCIs. **Conclusions:** RO5126766 has shown exciting preliminary activity across a wide range of Ras- and RAF-mutated malignancies, with significant dose rates in lung and melanoma. Of note, 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: NCT02516553.
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 (1%), an additional 9 of 83 (11%) evaluable pts at expansion had a partial response: 1 melanoma pt refractory to prior BRAF/MKI treatment, 3 NSCLC 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/485W gallibadder cancer. The duration of response ranged from 2 to 24+ months. In total, 4 pts (11%) with BRAF V600E mutant melanoma, 2 with BRAF V600E and non-V600E mutant solid tumors including melanoma, glioblastoma multiforme, lung cancer with brain metastases, gallibadder and head & neck cancer. These data support further clinical development of ulixertinib. Clinical trial information: NCT01781429.

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-drug conjugate (ADC) targeting 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 safety, pharmacokinetics (PK), pharmacodynamics (PD) and anti-drug antibody (ADA) responses including safety, PK, pharmacodynamics and preliminary anti-tumor activity by RECIST 1.1. Results: A total of 42 pts were 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) were enrolled. 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 Q2W 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 in pts 3 (Q2W) and 4 (Q3W) of 13 evaluable ABBV-221 treated pts had a PR (3 confirmed, 1 unconfirmed) with DOR 1+, 2+, 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. Response trends were similar in both squamous and non-squamous histology. Conclusions: ABBV-399 is well tolerated at 2.7 mg/kg once every 21 days and has the promise to advance into Phase II studies as a monotherapy and in combination with erlotinib. Updated efficacy/safety data and MET gene status will be presented. Clinical trial information: NCT02099058.

Background: ABBV-399 is a first-in-class ADC composed of a humanized mAb, a hydrazide 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 ABBV-647263 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 as monotherapy (QW, Cohort A) or in combination with erlotinib (AbbV-Erl; 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) were enrolled. 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 Q2W 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 in pts 3 (Q2W) and 4 (Q3W) of 13 evaluable ABBV-221 treated pts had a PR (3 confirmed, 1 unconfirmed) with DOR 1+, 2+, 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. Response trends were similar in both squamous and non-squamous histology. Conclusions: ABBV-399 is well tolerated at 2.7 mg/kg once every 21 days and has the promise to advance into Phase II studies as a monotherapy and in combination with erlotinib. Updated efficacy/safety data and MET gene status will be presented. Clinical trial information: NCT02099058.
Personalized, molecularly matched combination therapies for treatment-naïve tumors: The evidence

**Background:** Precision medicine has been studied in patients (pts) with advanced, heavily-treated cancers by administering molecularly matched therapies. 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-year mortality). Comprehensive genomic profiling (CGP; Foundation Medicine; 315 genes), and, if possible, PD-L1 IHC, tumor mutational burden (TMB) and circulating tumor DNA (ctDNA) were performed. A molecular tumor board discussed results immediately upon receipt, and emphasized customized combinations. Final decisions were made using 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%) were 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 (MS) for changes (#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: 1/3 by molecular matching rates (~36%); 2) high rates of SD (~53%); and 3) improved PFS. Study expansion is ongoing.

Clinical trial molecular matching rates (~36%); 2) high rates of SD (~53%); and 3) improved PFS. Study expansion is ongoing. Clinical trial molecular matching rates (~36%); 2) high rates of SD (~53%); and 3) improved PFS. Study expansion is ongoing.
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: Santanu Sarker, 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 effect. Six 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. Metabolic changes in urine and plasma correlated with preclinical 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 renal function, which were an expected on-target effect. The activity of AZD3965 is ongoing in tumours known to express MCT1. Clinical trial information: NCT01791595.

A phase I trial of TRC102 (methoxyamine HCl) with temozolomide (TMZ) in patients with solid tumours and lymphomas.

First Author: Robert S. Meehan, Early Clinical Trials Development Program, DCTD, 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 tumor cell line genetic characteristics, e.g., O6-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 TRC102 with TMZ in solid tumor patients (pts), to determine the RP2D and signals of activity. Antitumor responses were determined using RECIST 1.1 criteria.

Results: 44 pts (12 M:32 F median age 68) were enrolled in the expansion cohort. 5 pts were evaluable; three pts remain on study. 11/14 paired biopsies were analyzed for NQO1 staining intensity and prevalence. After 18 patients were treated, 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) of TRC102 was 390 mg/m2. The most common treatment-related adverse events were anemia (79%), fatigue (45%), hypoxia (33%), hemolytic (17%), nausea (17%) and vomiting (17%). Transient grade 3 hypoxia, due to methemoglobinemia patients. Among 31 evaluable patients, the most common treatment-related adverse events were anemia (n = 11) and progressive disease (n = 19). For the 18 analyzed cases, tumor response was assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1) criteria. Among 31 evaluable patients, the most common treatment-related adverse events were anemia (n = 11) and progressive disease (n = 19).

Conclusions: TRC102 with TMZ was well tolerated, with a number of dose limiting toxicities, including anemia, fatigue, neutropenia, nausea and vomiting. Numerous signals of activity were observed. A 3+3 dose escalation study of 3 schedules (weekly, every other week, or every 3 weeks) was conducted to determine the maximum tolerated dose (MTD) of TRC102. TRC102 with TMZ was not associated with reduced survival compared to historical controls and has ongoing activity in solid tumors. The combination of TRC102 and TMZ is being evaluated in a phase II trial of solid tumors.
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 (MEL) for the treatment of patients (pts) with relapsed/refractory (R/R) AML.

Methods: A phase (Ph) 1/2 trial in pts with R/R AML escalated GMI-1271 across pharmacologically active doses from 5-20 mg/kg combined with MEL. 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 MEL 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-Selectin binding, lack of DLT, and clinical outcomes. Ph1/Ph2 combined median age was 55 years (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 AE’s were febrile neutropenia (36%), sepsis (>26% back); leucopenia (13%), hypotension (13%), and d-dimer (13%), 7% respectively. ORR (CR/CRi/MS/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. Clinical benefit rate (CBR) was defined as CR + PR + SD ≥ 2 mos; 17% prior SCT; 55% unfavorable cytogenetics (by SWOG). Common Gr 3/4 AE’s were febrile neutropenia (36%), sepsis (>26% back); leucopenia (13%), hypotension (13%), and d-dimer (13%), 7% respectively. ORR (CR/CRi/MS/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-selectin antagonist, to MEL 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.

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 Aghdassi, 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 ≤ 2) were enrolled. Mandatory post and post induction 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 character-istics (safety, PK, and efficacy) of LY. Secondary objectives were to characterize the pharmacokinetics (PK) and 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%), hypoa-lbuminemia (40%), nausea (37%), AST increase (37%), anemia (34%), anorexia (34%), creatinine elevation (29%), and constipation (23%). Most common grade 3 (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-related fatalities were reported. One pt (adenoid cystic carcinoma) had stable disease (∼3 mos as of last visit), 19 pts had progressive disease, and 15 pts were not 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 re-lationship 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 macrophages (CD1c+CD14+CD33+). Indicating biologically relevant doses. Conclusions: RD2 for LY monotherapy has been determined. Detailed PK and PD data will be presented. Clinical trial information: NCT01346358.

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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 patients with solid tumors. ARQ 092 potentiated antitumor activity of P 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, on/5-6 days off)

Conclusions: Encouraging antitumor activity was demonstrated in heavily pretreated ovarian cancer pts, but full dose CP was not tolerated by most patients. Clinical trial information: NCT02476955.
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. Kauppa-statistics were used to analyze 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 [95%-CI: 0.912–1.0]) 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” (κ = 0.583 [0.541–0.624]) for individual TL, “fair” (κ = 0.440 [0.387 to 0.504]) for assessment of progressive disease, and “almost perfect” (κ = 0.966 [95%-CI: 0.912–1.0]) for the 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 preference for classification of patients as disease progressive or not.

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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 anti-tumor activity of TCA.

Methods: Data were collected from phase 2 and 3 clinical trials. Using an individual patient database (IPD), the 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. Food effect studies and drug label recommendations: A review of recently approved oncology products. First Author: Mark Farha, AstraZeneca, Waltham, MA

Evaluation of the effect of food on the pharmacokinetics of 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 30, 2016; abstr 2525), 2-h IV infusion on Days 1, 8, 15 (Q28d) of BAL101553 up to 80 mg/m² (maximum administered dose, MAD) showed vascular toxicities, including transient hypertension, which appeared to be Cmax related. The recommended Phase 2 dose (RP2D) was 30 mg/m² 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 Cmax related toxicity and improves the therapeutic window (NCT02490800).

Methods: Patients (pts) with advanced solid tumors who failed standard therapy, received QD oral BAL101553 (28-day cycles) in a 3+3 dose-escalation design to determine the MTD. Adverse events were assessed by CTCAE v4.0 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 G2/4 anemia 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) was compared to the RP2D of 30 mg/m² for 2-h IV was more than 5-fold higher (19,656 vs 3,584 ng*h/mL) and Cmax was 1.5-fold lower (171 vs 266 ng/mL). Both Cmax 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 Cmax levels compared to a 2-h weekly infusion, due to the absence of 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.
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 P13K/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 P13K/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 conducted parallel, 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 were 240mg 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, carcinoma, 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 nearly 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: Shriraj 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 = 4.10-12) and adenocortical carcinoma (45 mo vs NR, p = .03) and worse OS in low grade glioma (119 vs 64 mo, p = 6x10^-9). 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 (5 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), prostate (3 TPM), and lung adenocarcinoma (2 TPM). ER expression was associated with improved OS in mesothelioma (15 vs 26 mo, p = .33) 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 adenocarcinoma, sarcomas, 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 drug toxicity signatures: anthracyclines (n = 83,179), platinum (117,993), antimetabolites (n = 98,122), taxanes (n = 94,271), proteasome inhibitors (n = 44,681), immune checkpoint inhibitors (n = 33,864), Bruton TKis (n = 9,247), MEKis (n = 4,018), immunomodulatory agents (n = 34,457), anaplastic lymphoma Kis (n = 7,635), PI3K-AKT-mTOR inhibitors (n = 34,457), anaplastic lymphoma Kis (n = 7,635), PI3K-AKT-mTOR inhibitors (n = 33,864), Bruton TKis (n = 9,247), MEKis (n = 4,018), immunomodulatory agents (n = 174,810), proteasome inhibitors (n = 44,681), immune checkpoint inhibitors (n = 20,287), Pharmacovigilance metrics (Relative Risks & safety signals) were used to establish statistical correlation & toxicity signals were differentiated using the Kolmogorov-Smirnov test.

Results: To validate the use of the AERSMine to detect AE’s, we focused on cardio toxicity, it identified classic drug associated AE’s (e.g. ventricular dysfunction with anthracyclines, HER2is & 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, paralysing 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 participating sponsors 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 hematologic 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. and Canada) and 8.4% (14,975) from Asia. Countries in Latin America, Middle East/Africa and the Atlantic 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.

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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 PD assays.

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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 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 investigated using logistic regression analysis. Results: Of 2819 patient-weeks, pertaining to 169 patients treated on 132 trials (69%), 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 use of opioids or anti-emetics were not 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 3.035, 95%CI : 1.051-8.821, p < 0.05) were independent significant factors. 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.
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 refined 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 hospitalizations in QD vs. QDx5 were 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.

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A study of vistusertib in combination with selumetinib in patients with advanced cancers: TORCEMA phase Ib results. 

**Methods:**

A novel technique to obtain multiple bx from single metastatic lesion in pts with advanced malignancies using a radiologically-guided single-pass percutaneous technique. 

**Background:**

First Author: Valerie Heong, National University Hospital, Singapore, Singapore

 actionable truncal mutations (ATMs) in patients (pts) with advanced solid tumours. In 1 pt, only 2 of 4 cores were successfully sequenced. The other 3 cores were omitted from analysis due to poor quality DNA with 13 pts successfully sequenced. 

**Results:**

Median of 4 core bx were obtained in 1/4, 2/4, 3/4, and 4/4 bx cores was 63(16-91)%, 5(1-65)%, 4(0-30)%, respectively, suggesting significant subclonal diversity within a single lesion. 

**Conclusions:**

**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 actionable truncal mutations (ATMs) in patients (pts) with advanced solid malignancies using a radiologically-guided single-pass percutaneous technique. 

First Author: Valene Heng, National University Hospital, Singapore, Singapore

First Author: Ignacio Melero, CIMA, CUN, University Navarra, Centro de Investigacion Biomédica en Red de Oncologia (CIBERONC), 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. 

Pharmacokinetics (PK) and pharmacodynamics (PD) of a novel carcinoma- bryonic 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 Investigacion Biomédica en Red de Oncologia (CIBERONC), Spain

**Background:**

First Author: Peter Schmidt, Barts Health NHS Trust, London, United Kingdom

**Methods:**

EGFR_T790M ATM were treated with an EGFRT790M specific TKI.

**Results:**

15 pts (5 NSCLC, 5 breast cancer, 2 uterine and 1 cervical and 1 adenocarcinoma) with actionable truncal mutations (ATMs) were enrolled into 2 cohorts in a dose expansion phase (DEXP). Cohort 1 (C1) was recommended phase II dose. 

**Conclusions:**

The primary endpoint was DLTs. Based on DLTs, dose intensity and cumulative toxicity, the intermittent schedule I3C was selected as RP2D for expansion cohorts. 

**Background:**

**Methods:**

Aptivus plus crizitinib in patients with advanced solid tumors and metastatic renal cell carcinoma (mRCC): Preliminary phase 1b results. 

First Author: M. Dorr Michaelson, Massachusetts General Hospital Cancer Center, Boston, MA

**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) + C2 200 mg Bid (n = 5); AX 3 mg Bid + C2 250 mg Bid (n = 3); AX 5 mg Bid + C2 200 mg Bid (n = 4); or AX 5 mg Bid + C2 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 ≥2 pts; 1 pt had a Grade 5 AE (disease progression). 

**Conclusions:**

**Background:**

**Methods:**

For the continuous schedule, 2 out of 9 patients treated at dose level C2C 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: 4.0-fold, n = 20; CD8/CD3: 1.7-fold, n = 15) without dose-dependence. In S2, preliminary data of T cell density (5-80ng) were similar to S1 (2-fold). In S1, a significant correlation was observed between intermittent (I3C) and continuous (C2C) schedules 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 CD T cells (HLA-DR/Ki67) but not of CD8, 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. 

**Results:**

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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 systems were 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 DL (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 frequentest AEs were nausea, vomiting, decreased appetite, constipation, diaphoresis, pyrexia, fatigue, and rash, all seen in > 20% of pts. No discontinues 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.

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 camptothcin top1 inhibitors, with better chemical stability (lacking the labile hydroxyalcohol 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 camptothcin-resistant cell lines and mouse models, as well as in cells that were overexpressing the ABC (ABC) transporters, a common characteristic of 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 (NCT0275576), 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 analysis (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 and on days 2–8. Response is defined by RECIST 1.1 on Day 1. 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/m², DL7 myelosuppression). Common Grade 3/4 adverse events by CTCAE v.4 included anemia (5 pts, 15%), thrombocyto- penia (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 >4 months, with 4 pts >12 months. Conclusions: LMP776 is overall well tolerated. Explorative correlates and additional trials are being considered. Clinical trial information: NCT01051635.
Patterns of failure on Ga PSMA (GaPSMA) and F18 FDG (FDG) PET CT in a phase II trial of 112 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 PSMA response rates in men undergoing treatment. 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 characteristic patterns of failure, to determine optimal future tx strategies.

Methods: Men with mCRPC who had failed androgen blockade, failed/progressed biochemically during LuPSMA tx and had evaluable studies were included. Imaging was performed with serial GaPSMA and FDG PET-CT scans before, during, and after discontinuation of therapy. Treatments were sulfate-free ILT (bicalutamide 500 mg orally). Patients were monitored for changes in tumor burden by CT-volume before, during, and after discontinuation of therapy. Three pts had disease progression (PSMA +/FDG+ lesions), while the remaining 8 had sustained progression.

Conclusions: PSMA acts as both a target for radionuclide therapy and biomarker for effective tx response. PSMA and FDG imaging at PSA failure following or during LuPSMA therapy identifies phenotypic patterns of failure that have implications for determining next best tx options in men with mCRPC.

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Results: Eligible pts had advanced colorectal cancer, suitable for 177Lu*-line FOLFIRO: Bevacizumab. Pts had blood analyzed by Affymetrix DME™ Plus Array and additional SNPs were genotyped. For HNI, pts were given IV 250MBq 99mTc-IDA and imaging analysis on day 1 cycle 1, PK parameters derived by non-compartmental analysis. Statistical correlations were evaluated between (i) IDA HNI and (2) PKs, with IR PK, toxicity, objective response (ORR) and progression-free survival (PFS). Results: 32 pts analyzed, 31 pts completed 4 cycles. (1) PK correlates: (a) HNI CL and 1hRET with SN38 Metabolic CL (P = 0.04) and (b) HNl DeCI with IR AUC0-1 (P = 0.04). (2) Grade 3+ diarrhea (N = 4, 13%), grade 3 neutropenia (N = 3, 10%), grade 3 liver toxicity (N = 2, 6%) and grade 3 elevated transaminases (N = 2, 6%). (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 genotypes (P < 0.05). (5) PK by SN38 PK exposure, MTHFR 677C > T, HNI CL, HNI HEP and variants in SLC22A2, SLC7A7, CHST1, UGT1A1, -2B7, ABCB1. (6) S colonic perforation (N = 1, 3%). (7) S esophageal perforation (N = 1, 3%). (8) Grade 3+ treatment-related death (N = 1, 3%). (9) Grade 3+ G3. In these patients, we researched the other 3 SNPs (c.2846 A > T, c.1679T > C, c.1677A > C). Mutational status was analyzed with real-time PCR. The aim of this study is to confirm that the detection of additional polymorphisms in HNI could enhance predictive pharmacogenomics. In 2011, we began to screen DPYD*2A 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-NGI V.3 toxicity of G3. In these patients, we researched the other 3 SNPs (c.2846 A > T, c.1679T > C, c.1677A > C). Mutational status was analyzed with real-time PCR. Results: From 2011 to 2016 we pre-emptively screened DPYD deficiency in 1,863 patients and 32 subjects (1.5%), 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 (1.2%). Of the 541 wild-type cases, 114 presented toxicities ≥ G3 (19% of patients) and 88% of patients had 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, Azienda Ospedaliera Santa Maria Nuova – IRCCS, Reggio Emilia, Italy (2), sanita (2), sarco (2), 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 1 pt 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%). Severe adverse events (SAEs) related to study drug were reported in 4 pts: diarrhea (1 pt, 70mg QD; 1 pt, 80mg QD), nausea and vomiting (1 pt, 70mg QD), and diarrhea, nausea and vomiting (1 pt, 80mg QD). Stable disease has been observed in 7 pts up to 24 weeks, in which 2/28 pts (7%) achieved tumor shrinkage. Conclusions: Based on the present data, KPB-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.
**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-1 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 objective response rate (ORR) and best percent change in target lesion from baseline per BICR assessment. Safety endpoints included Grade 3+ AE (any AE, drug-related AE, AEs, drug-related AEs) 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 0.25 to 0.74). 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 a single agent in UC patients. Overall, no relationship of PK exposure with the 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 0.25 to 0.74). 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.

**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 OPTIFLIV). First Author: Francis Levi, Cancer ChemoTherapy Unit, Warwick Medical School, Coventry, United Kingdom

Background: The HAI of Irinotecan-Oxaliplatin-5-Fluouracil (IFO) with IV-Cet achieved 29.7% complete uLM-CRC responses (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 pharmacogenetic genes were analysed in blood mononuclear cells (ADME PGx, MassARRAY platform, Sequenom, USA). Relations between SNPs and tumor response, RO+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 3rd-4th line (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-g 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 RO-R1 resection rate. Statistically significant (p < 0.05) of SNPs on PK parameters show that systemic formation: NCT00852228.}

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**2570** Poster Session (Board #62), Mon, 8:00 AM-11:30 AM

A novel phase I study of AZD8186, a potently inhibiting 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: AZD1412 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 until progression, unacceptable toxicity or maximum tolerated dose was reached. Results: Dose limiting toxicities were observed at 100 mg BD. 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 pharmacogenetic genes were analysed in blood mononuclear cells (ADME PGx, MassARRAY platform, Sequenom, USA). Relations between SNPs and tumor response, RO+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 3rd-4th line (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-g 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 RO-R1 resection rate. Statistically significant (p < 0.05) of SNPs on PK parameters show that systemic formation: NCT00852228.

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**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 cancers 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 high-grade serous ovarian cancer (HGSOCS). Methods: In the dose escalation part, weekly P 80mg/m² (IV) (67 weeks) was evaluated in in combination with weekly/V in 2 schedules of V; Schedule A: V (25, 50 or 75mg) PID PO on day(0)-1/week and Schedule B: V (75 or 100mg) PID PO D1-2/week. This was followed by an expansion cohort in 25 HGSOCS patients. Results: Dose limiting toxicities in Schedule A were fatigue and rash in the combination of V and P 75-250mg/m². In Schedule B, rash and fatigue. The AUC, Cmax and half-life of V in the 50mg-cohort were 2821ug.h/ml, 926ug/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 = 0.0459). 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/m² D1 and V 50mg BID D1-3 for 6/7 weeks. In the HGSOCS expansion, 96% of patients had relapsed within 12 months of last platinum/tegafur 100% on study for > 1 year. 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. Preliminary findings of the safety/tolerability and preliminary efficacy in combination with vistusertib or abiraterone acetate is encouraging. Clinical trial information: NCT01884285.
Investigating novel resistance mechanisms to third generation EGFR TKI osimertinib in non-small cell lung cancer patients using next generation sequencing. First Author: Qiaoxiang 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 who were clinically resistant to osimertinib. Results: In addition to the notable EGFR C797V 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 mutation alternations 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. Integrated 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 C797F-, L792- and L718-wild type.

A Phase I multi-center, open-label study. 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 dose escalation design. Tas was given continuously 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 mg (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 grade 3 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 biweekly exposure 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.

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 PI3K-m class 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. 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); MFI 11/13, median lines prior therapy. 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/G5 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 PIK3CA mutation. No DLTs were recorded in other key genes such as KRAS, H1047R mutant breast cancers (100%) median decrease in pAKT and pGSK3β, pERBB2 and PIK3CA, with addition of ET in dose expansion. Notably, all Pts had ongoing RECIST partial response; 1 pt with PIK3CA E545K 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.
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 lower 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 (TubBHi). EC1456 binds to, and is endocytosed by the FR-expressing cancer cell to deliver TubBHi. 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); QDX (continuously weekly). QW (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 99mTc-etarfolatide-selected NSCLC patients in up to 3 cycles. Results: 74 pts are evaluable for toxicity. Median age is 68 years (range: 26-88); 53 pts are female. Toxicities are primarily Grade 1 and 2. Common grade 3/4 adverse events (AEs) were papular rash. 2/2 treatment-naïve pts had a PR (1 melanoma, 2 lung). One lung pt remains in PR at 2 months and the other has an uPR at 1.2 months.

Conclusion: All Part A EC1456 schedules have been well tolerated. RP2 dose and schedule of 12.5 mg/m² QW and 10.0 mg/m² CWD). TRAEs are summarized in the table for each NSCLC population (Part B) is ongoing. Clinical trial information: NCT01999738.

2576 Poster Session (Board #68), Mon, 8:00 AM-11:30 AM

2577 Poster Session (Board #69), Mon, 8:00 AM-11:30 AM

A phase la 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 hyperpnea (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 (fatigue, nausea), gastrointestinal (diarrhea, vomiting, diarrhea), hepatic (transaminase elevations) and neurologic (dizziness, gait disturbance, paresthesia) 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 Cmax 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.

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 T cell 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 660 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 commonly observed adverse events (AEs) included nausea (47%), vomiting (47%), dyspnea (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 120 mg based on the occurrence of Grade 3 transaminase elevations (n = 2) and hyperpnea (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 (fatigue, nausea), gastrointestinal (diarrhea, vomiting, diarrhea), hepatic (transaminase elevations) and neurologic (dizziness, gait disturbance, paresthesia) 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 Cmax 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.

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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 xenograph models, via multiple MOAs including induction of cancer cell cycle arrest and apoptosis, and reducing vascular 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 administered 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 (500 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. While no correlation was observed between onset (5–7 days) and conversion 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 and lower dose level, and some patients have experience with clinical benefit. Clinical trial information: NCT02507544; NCT02703298.

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 actionable cancer-related mutations 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%), metastatic 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. Among the patients with identifiable mutations, the most common were PIK3R1 (8%), CDKN2A/B (7%), and PI3K (7%). Thirty-six patients (38%) had at least one potentially actionable alteration in 21 different tumors (eg: PI3K in metaplastic breast and adenoid cystic carcinoma). Eighty-seven out of 96 patients (92%) had at least one potentially actionable alteration in 21 different tumors (eg: PI3K in metastatic breast and adenoid cystic carcinoma and BRAFV600E in Ermsderm-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 GCP 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.

Molecular markers to predict response to selective fibroblast growth factor receptor inhibitors (FGFRinh) in patients with (pt) BRAFV600E mutant (mut) tumors. First Author: Cinta Hierro, Medical Oncology Department, Vall d’Hebron University Hospital, Molecular Therapies Research Group, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Several FGFR and ligand (11q) alterations have been described in cancer. While FGFR2 and FGFR3 high expression (mRNAh) or FGFRmut predict sensitivity in the clinic, Methods: Retrospective analysis of pts with molecularly-selected FGFRmut and FGFRmRNAh/muts treated with FGFRinh in phase 1 trials at our institution. Mut were detected with IlluminaO or FoundationOneO. FGFR1-2-3amp were analyzed by in situ hybridization and mRNA levels by qRT-PCR or nCounterO. 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 (4), esophageal (3), liver (3), lung (3), others (7). Median TTP was 1.67 m (CI 95% 1.40-2.87). In the FGFRmRNAh/muO population (30), 7 pts achieved ClinBen (23%). 4 out of these seven pts had mRNAm (1 FGFR2-3amp breast with FGFR2 mRNAh, 1 bladder FGFR3 mRNAh and 2 liver FGFR4 mRNAh without amp). Clinical benefit (Cl) was defined as with TTP < 2 yrs. Of the remaining 5 unresponsive FGFRmRNAh pts had subclonal events, some of these FGFRmut were of unknown functional significance, and had coexisting oncogenic mut in MAPK or PI3K pathways. Conclusions: Our results suggest that ClinBen with FGFRinh in the FGFRamp setting is observed in pts with high mRNA expression and/or ligand co-amplification, and in the FGFRmRNAh population may be dependent on clonality and potential of the event and co-existence of driver mut.

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) 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, 1 pt achieved ClinBen (with heavily-pretreated breast cancer with HER2 amplification (2) or HER2mut (11) stable disease (SD) 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 was 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 inhibitor 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 (≥ 20%) were vomiting (32%); anorexia and fatigue (31%); dysgeusia and constipation (25%). ETC-159 Cmax increased with dose with a mean t 1/2 of 14hr. 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 p-CTX levels was first observed at 4 mg and at C1015 in some patients. PD modulation increased with dose, consistent with on-target modulation of Wnt signalling. Two pts had p-CTX rise > 1000 pg/ml (reference limit) and a ≥ 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 carcinomatosis) 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. p-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.

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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: Akosa 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 VEG-F-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 noted in 23 (59%) 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 imiprimine 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 imiprimides. 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 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 3/5/5mg and escalated to 625mg using an ascending dose schedule. We determined 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 625mg. 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 in 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 IIb study of the combination of selumetinib (AZD6244, ARRY-142866) 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, to date, as is necessary 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 models. We conducted an NCI CTEP-approved Phase IIIB 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 who continue on study to date (112 weeks and 145 weeks). The primary endpoint was to determine the RP2D of selumetinib and CsA combination. Based on the exceptional safety profile 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. FD2 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 alterations in diverse cancers: Next-generation sequencing of 539 patients. First Author: Roman Grosberg, 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 PRCC2 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, SMARCBI). 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 (66%), had a strong family history of cancer (80%) & were smokers (42%). The most common mutated subunit was ARID1A (50%) followed by PBRM1 (36%), ARID2 (12%), SMARCA4 (12%), and SMARCBI (10%). **All mutations were predicted to be inactivating.** Actionable co-occurring pathway alterations ARID1A and NOTCH1/2 (10%). The majority of patients (62%) were enrolled on a trial predicted to be inactivating.

**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 antimitabolite 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), breast cancer (BC), cervical cancer (C)) 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 18F-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. **Conclusion:** 18F-FDG-PET/CT imaging demonstrated partial metabolic responses in 3 patients at the 0.5 mg/kg and one patient at the 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 11 (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 finding: NCT012573660.
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 maximal tolerated dose (MTD), and recommended phase II dose (RP2D).

Methods: A modified accelerated-escalation 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/wk to 1875 mg/wk. Key eligibility: advanced/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/#s 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 reached. No DLTs observed. Tumor types: B CRC, 3 pancreatic, 2 sarcoma and 1 each cervical, endometrial, NSCLC (adenoc) and small bowel. Of 17 pts, 10 (59%) had ≤1 br-related adverse events (AE), 6 (35%) had ≥2. No DLT (n=2), possibly related: M0 (fatigue (9,53%), anorexia (5,29%), nausea (4,24%), vomiting (4,24%), Gr2. One of 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 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 ongoing.

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.

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) signalling is implicated in carcinogenesis and is associated with poor prognosis in multiple tumour 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 results of our 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 weekly paclitaxel 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 at the new dose escalation (400mg). MTD and RP2D were reached. After the DLT period 2 patients developed G2 and 4 DLTs observed in first 3 pts. Taladegib was escalated to 20 mg where 2/6 had a DLT (Gr3 neuropathy (n=2); Gr3 neuropathy (n=1)). Grade ≥3 TRAEs (≥3% of final DNA sample is 130s Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics

Methods: DLTs 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 were observed in first 3 pts. Ali was escalated to 20 mg where 2/6 had a DLT (Gr3 neuropathy (n=2); Gr3 neuropathy (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%), mostly ≤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/m²) + continuous 5FU (D2-4, 2400 mg/m²). The combination was tolerable, and preliminary clinical activity was seen in a majority of pts. Consecutive biomarker studies to evaluate AURKA target inhibition are ongoing and will be reported. Clinical trial information: NCT02319018.
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 PDGFRA antagonist, is a targeted human IgG1 monoclonal antibody that specifically binds PDGFRA, 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. This 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 cohorts). Secondary objectives (Phase Ia) 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 ≥ 12 weeks. Clinical trial information: NCT02819999.
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 0–2, 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 dose-finding phase. Primary objectives are to determine the maximum tolerated dose (MTD) of COH29, toxicities per GCTEx4, and cellular apoptosis. Secondary objectives include assessment of objective response per RECIST 1.1 every 2 cycles, PD assessments include circulating tumor cells. PK profiles are assessed throughout the study. Dose levels to determine degree of cellular apoptosis, evaluation of dNTP pool alterations, and assessment of tumor response to COH29. Clinical trial information: NCT02112565.

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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 is overexpressed in 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-treated tumor cells, and demonstrated synergistic anti-tumor activity when combined with conventional chemotherapy. EPHARNA undergo GP II 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: 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 priority. All patients (dose escalation and dose expansion phases) must be willing to undergo pre- and post-treatment biopsies. For dose expansion of dose escalation part and a phase Ila expansion part. The dose escalation part explores two different dose 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 predefined 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 Ila 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.

A phase I, first-in-human, dose escalation trial 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 a auristatin-based cytotoxic payload (AF-HPA). An average of 12 AF-HPA molecules is conjugated to each antibody via a bioadaptable 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 step (DES) and an expansion step (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 chemotherapies 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 tissue sample 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.

A phase I study of SRA737 (formerly known as CT245737) administered orally in patients with advanced cancer. First Author: Maxime Chenard-Poirier, CHU de Quebec-Universite Laval, Quebec, 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 (e.g., MYC and RAS) combined with loss of function in tumor suppressors (e.g., 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 multiple dose trial 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 in 1Q3W 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 predefined 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 Ila 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.

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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 monitor the safety, tolerability, and pharmacokinetics of nanoparticle encapsulated Aurora B kinase inhibitor AZD2811 in patients with advanced solid tumours. First Author: Howard A. Burns, 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 (Rodier 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-970 intravenously (IV) on Days 2 and 9; Veliparib orally twice daily (q12h 100 mg) on Days 1 and 8; Cisplatin 40 mg/m2 on Days 1 and 8 (21-day cycle). Patients are treated with 3 cycles and followed for 6 months. Key eligibility criteria include solid tumors 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.

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: Multiple 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 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 antibubulin therapy with paclitaxel or erubulin in patients with metastatic breast cancer (MBC). First Author: Jesus Del Santo Anampa Messias, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY

Background: TMEM (Tumor Microenvironment of Metastasis) is a micro-anatomic structures formed by a Mena-expressing tumor cell, Tie2-expressing macrophage, and endothelial cell in direct contact, 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+/VEGFP+ macrophages upon binding of the VEGF receptor to angiopoietin. The Tie2 inhibitor rebastinib (R) stabilizes 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 erubulin (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 (NCT02824576) 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 (day 1 and 8) for four 21-day cycles. Key eligibility includes histologically confirmed HER2 negative MBC, ≥ 2 non-targeted from trial, well-preserved organ systems, ECOG PS 0 to 1 and available tumor tissue for further analysis. Tissue biopsy after two treatment cycles in 6 patients will be performed to evaluate TMEM score and function. Pharmacodynamic biomarkers to be measured during cycle 1-3 include CTGs, 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. If ≥ 2 DL of rebastinib, and ≥ 3 patients at each DL, it is anticipated 6-12 patients will be required. This trial has enrolled two patients assigned to P arm combined with R 50mg BID. Clinical trial information: NCT02723864.
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 CEBP-α (CCAT/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 CEBP-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 hematologic, 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 CEBP-α mRNA levels in PBMCs and optional tumor tissue, evaluation of CEBP-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 Inglês 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 (e.g. MYC and RAS) combined with loss of function in tumor suppressors (e.g. 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, 5, 9, 10, 16, 17 of each 28-d cycle. Eligibility criteria include WHO performance status of 0-1, age >18, ECOG PS 0-1, systemic tumors known to have Chk1-sensitizing aberrations (e.g., 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.

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FGFR alterations, including mutations and fusions, drive oncogenesis. PRN1371 is a highly selective oral, irreversible covalent FGFR1-4 kinase inhibitor, in patients with advanced solid tumors, including squamous cell carcinomas of the head and neck. 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 FGFR23 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.

**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 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 FGFR23 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.

**Background:** Tipifarnib is a potent and highly selective inhibitor of farnesyl transferase (FT). FT catalyzes the post-translational attachment of farnesyl groups to signaling proteins that are requisite for localization to the inner 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 designed 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 trial, 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.

**Background:** Tipifarnib (MPS1), a dual-specificity serine-threonine kinase, is a target 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 other kinases.Robust suppression of tumor growth was 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 of clinical response. A total of 80 patients (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 ≤ 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.
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. 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_{0-12h} 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_{0-12h} 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 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_{0-12h} is increased in subsequent cohorts until exposure limiting toxicity occurs. Main objectives are to assess safety and establish the maximum tolerated exposure, personalized dose titration based on the sorafenib plasma AUC_{0-12h} 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: Wang X. et al. J Transl Med 2011;9:220. Clinical trial information: NCT026536426.
Epacradostat plus nivolumab in patients with advanced solid tumors: Preliminary phase II/I 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, SCCCN, 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 (SCHCN, 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 2% (E 100 mg) and 13% (E 300 mg) of pts. There were no TR-deaths. For the 23 recently enrolled, efficacy-evaluable SCHCN 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. Of E 100 mg, 5 (19%) pts were treated with E 100 mg in E 300 mg. Of E 100 mg, 52% (n = 2) 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 SCHCN and MEL pts. Updated data will be presented at the meeting. Clinical trial information: NCT02327078.
Background: Adenosine production in the tumor leads to immunosuppression through A2AR on infiltrating immune cells. CPI-444 is an oral A2AR antagonist. A2AR is expressed by single agent (SA) anti-tumor activity in preclinical models. This phase 1/2b clinical trial uses a 2-step adaptive design to evaluate CPI-444 as a SA and in combination (combo) with the anti-PD1 antibody, atezolizumab (atezo). We report results of RCC and NSCLC cohorts. Methods: Primary objectives: safety, efficacy, and to identify optimal dosesschedule. 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 eligible 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 grade 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 IV q2 weeks and atezo 840mg IV q2 weeks. The disease control rate (DCR, CR+PR+SD; duration 3 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 18 evaluable RCC pts, 1 PR (PD1 negative pt) and 8 SD were seen, and 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 PD1 negative can also benefit. Clinical trial information: NCT02655982.

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 cancer (RCC) and non-small cell lung cancer (NSCLC) patients. First Author: Lawrence Fong, University of California, San Francisco, San Francisco, CA

Primary objectives: safety, efficacy and to identify optimal dosesschedule. 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 eligible 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 grade 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 IV q2 weeks and atezo 840mg IV q2 weeks. The disease control rate (DCR, CR+PR+SD; duration 3 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 18 evaluable RCC pts, 1 PR (PD1 negative pt) and 8 SD were seen, and 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 PD1 negative can also benefit. Clinical trial information: NCT02655982.

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 anti-PD-1 checkpoint inhibitor in patients (pts) with solid tumors. First Author: Kynakos 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 arginase 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 arginase, 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 (tmax = 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 3.5±2.5 μM and 4.5±2.5 μM, respectively. CB-1158 inhibited arginase activity, and plasma arginase 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 arginase, 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 II (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, -2, and -3 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 drug-related TEAEs, BP and colitis responded well to steroids. Colitis and BP resolved (Grade 1, 2 months). One pt 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 a drug-related SAE of hypoglycemia (Grade 1). Three pts had treatment-related biomarkers. 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 M1S low [LO], CRC M1L V, and CRC M1S V); 1 CR from CRC M1S V, and 1 CR from CRC M1L V and OVA (10 mg/kg V, uPRL). 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.

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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 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 in R vs NR pts were noted (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 observed. Grade 1-2 toxicities and no grade 3-4 adverse events were noted, and WGS revealed differential metabolic signatures in R vs NR. Furthermore, diversity (p = 0.005; HR = 7.6) and abundance of specific gut 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 potential far-reaching implications, though results need to be validated in larger cohorts across cancer types.

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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), urthelial carcinoma (UC), triple-negative breast cancer, squamous cell carcinoma of head and neck (SCCHN), cervical cancer, hepatocellular carcinoma, and advanced melanoma pts with 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 pts (55%) discontinued study treatment, primarily due to disease progression (37%). 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.

3014 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

Activity of a novel immunotherapy combination of intralesional Cossaxicin A21 and systemic ipilimumab in advanced melanoma patients previously treated with anti-PD1 blockade therapy. First Author: Desiree Schmitz, Providence Cancer Center and Earle A. Chiles Research Institute, Portland, OR

Background: CAVATAK is a novel bio-selected oncolytic and immunotherapeutic strain of Cossaxicin A21 (CVA21) that when injected into melanoma lesions can increase immune-infiltration, up-regulation of 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 immune cells to follow CTA-4 blockade. Methods: This open label, phase 1b 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 10^9 TCID50 CVA21 i.t. on study days 1, 3, 5, 8 and 22, and then ipi for a further 6 series of injections. Ipi (3 mg/kg) ipi 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 (p=0.001), respectively. 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 asessment (irWHO criteria at Day 106) we observed a confirmed BORR of 38.0% (3/8) and a dCR (CR+PR+SD) of 96% (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.
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 these groups, with a p = 0.0064; Pearson’s chi-squared test) 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 melanoma patients with rapidly altering alterations in ARID2 – a closely related chromatin remodeling - 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 ccRCC 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.

FDA analysis of patients with baseline autoimmune diseases treated with PD-1/PD-L1 immunotherapy agents. First Author: Chana Weinsbok, 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 disease enrolled in 22 clinical trials of PD-1/PD-L1 immunotherapy agents 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 demographic data, comorbidities, and autoimmune diseases at baseline, duration of dosing, immunity-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. Patients with autoimmune diseases treated with PD-1/PD-L1 immunotherapy agents were identified. Of 51 adult pts with autoimmune diseases at baseline, 45 developed irAEs while 14 pts developed worsening of underlying autoimmune disease. Conclusions: FDA analysis of patients with baseline autoimmune diseases treated with PD-1/PD-L1 immunotherapy agents indicates that these agents are generally safe in patients with autoimmune diseases. However, a greater understanding of how to best manage the incidence of irAEs in this population is needed.

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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: Biandra Santamoro, 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 cerebral and peripheral 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: Neuroradiologic images were collected before and during CAR T cell infusion. We tested whether germline immune-specific eQTLs also impact IT outcome in adult patients with relapsed or refractory B-ALL (R/R B-ALL) treated with CD19 CAR T cells. Results: 21/51 treated pts developed sNTX (grade ≥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 brain (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 = 0.001). The proteins 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 thalamus, dorsal pons, and medulla. Conclusions: NTX is predominantly reversible. MRI findings suggesting transient toxicity to different grey structures and findings of a CSF-specific cytokine profile expand our knowledge of the etiology of NTX and may point toward 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 = 4.295, p = 0.0171) and rs9484988 (OR = 0.3328, p = 0.0271). Conclusion: In this study we report that rs6673928, an eQTL from the IL19/IL10 locus previously shown to predict autoimmune disease 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.
Cytokine release syndrome (CRS) and neurotoxicity (NT) after CD19-specific chimeric antigen receptor (CAR)-modified T cells. First Author: Cameron John Turner, 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 (NCT01865617) 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 =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 =4) and gr =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 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 hypoaalbuminemia. 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.

PRKDC: A new candidate for checkpoint blockade immunotherapy. First Author: Ming Huang Chen, Taipei Veterans General Hospital, Taipei, Taiwan

Background: Immune 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 immune checkpoint blockade therapies 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 found a significant correlation between PRKDC mutation status and 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 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 gain expression in CIXCL9, CIXCL10, GZMA and PRF1, compared to MSS patients (p = 0.0016, 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.
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 (multorgan 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 cytopoenias (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.

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.

Results: We report on the relationship between 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 cleared tumor biopsies (bx) from a subset of pts. Free/total OX40 expression was determined using both Chi2 and Cox analysis. Results: 46 (40%), 44 (38%) and 25 (22%) patients experienced PR, SD and PD to first-line platinum-based chemotherapy. 29 (22%), 34 (29.5%), 56 (48.5%) experienced PR, SD and PD to nivolumab. 59.5% (53/89) of patients who experienced clinical benefit (SD+PR) to first-line also experienced clinical benefit to nivolumab while only 20% (5/25) of patients with PD as best response to chemotherapy experienced 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 as well as baseline (BL) and Wk6, by immunohistochemistry. Results: 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 k67 and HLA-DR/CD38 expression in peripheral CD4+ central memory T cells. PT1, PT2 and all pts at ≥0.3 mg/kg had increased levels of PFS on nivolumab (median PFS not reached). 53/89 patients were 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 increased 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 PK are positive with treatment and correlate with PD 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 antibody clones for the detection, sheep anti-rabbit IgG DyLight800 was used.

**Results:** Epitope 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.

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3029 Poster Session (Board #124), Mon, 8:00 AM-11:30 AM

**Overall survival prognosis of patients in immune-ontology 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.

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99mTc-IL2 was purified by reverse-phase chromatography and diluted in 5% glucose with 0.1% human albumin before injection. Five patients were enrolled in study 1108 during durvalumab treatment. Nonparametric correlations (Spearman’s rho) were evaluated between OS, maximum percent change in target (r = 0.38, p < 0.0001) and non-target (r = 0.33, p < 0.0001) lesions, and OS in UC also correlated with increased ALB (r = 0.50, p < 0.0001). OS in UC also correlated with increased ALB (r = 0.50, p < 0.0001). 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 0.03 mg/kg and JTX-2011 related diarrhea at 0.1 mg/kg. Grade 1-2 AEs in ≥ 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 t1/2 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 naïve patients, lower than linear 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 (TTP). There is a need for biomarker techniques to discriminate pPROG (effect of therapy) and TTP (therapy failure). Nuclear medical imaging with radiopharmaceuticals capable of imaging immune cells; images can be fused to tumor types. Durvalumab is a human monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 and CD80. The results 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, hematologic categories TIL imaging with 99mTc-IL2 OS was similarly correlated with increased ALB (r = 0.45, 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), and decreased CL 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  
Metabolic 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 kyurenine (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 value = 0.0099 and p-value = 0.003 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 metabolic analysis of peripheral blood from nivolumab-treated patients, we find that the change in kyurenine 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, leading to an increased presence of UC in low/reduced expression regions. Tumor 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 ≥50% 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, type 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 DFS (HR 0.3; p = 0.005) and OS (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 = 0.0002). RCC NCT02087423 and NCT01693562 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+/IC+ pts, 36% in TC-IC+ pts, and 7% in the TC-IC- pts. Conclusions: IFNGS predicted improved outcomes in a cohort of 62 LUMC 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 provide rationale for TC+ inclusion (in addition to IC+) in the SP623 PD-L1 scoring algorithm for UC. IFNGS is an additional potential predictive biomarker in UC pts that warrants further investigation.

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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 tumor IFNG mRNA expression had improved survival (ORR, DFS, OS) to the anti-PD-L1 therapy durvalumab (D). To explore the relationship between IFNG expression and tumor response, we used a recently developed classifier to identify responders to durvalumab therapy.
Methods: We obtained fresh tumor biopsy samples from 105 pts enrolled in a multicenter phase II trial of durvalumab (10 mg/kg IV q2weeks) vs placebo in pts with refractory NSCLC. Genomic RNA was extracted from samples using the VAHTS Cancer RNA-sequencing Library Kit. We performed RNA sequencing on 48 pts (84% evaluable) and validated the classifier on an independent cohort of 57 pts (92% evaluable).
Results: In the validation cohort, we observed a 23% increase in ORR (p = 0.0014) with durvalumab compared to placebo. We identified a gene expression classifier that predicts responders to durvalumab with 100% sensitivity and 82% specificity. The classifier is based on changes in expression of IFNG and its mediators.
Conclusions: Our results provide evidence for the development of a predictive biomarker for response to durvalumab. Further validation in larger cohorts is needed to confirm these findings.

3042 Poster Session (Board #137), Mon, 8:00 AM-11:30 AM
CD133-directed 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: CD133 is an attractive therapeutic target for cancers. CD133 is expressed high in tumor stem cells in many types of tumors. CD133 expression is regulated by genes and proteins. We hypothesized that CD133 is a potential target for cancer therapy.
Methods: We developed a new CD133-directed chimeric antigen receptor (CD133-CART) to target CD133+ cells. We used the CD133-CART to treat patients with advanced and metastatic malignancies. We also evaluated the toxicity and efficacy of CD133-CART.
Results: In a phase I/II clinical trial, we treated 15 patients with CD133-CART. The overall response rate was 60%, and the complete response rate was 40%. The toxicity was manageable, with grade 3-4 adverse events occurring in 20% of patients.
Conclusions: CD133-CART is a promising therapeutic approach for patients with advanced and metastatic malignancies. Further studies are needed to evaluate its efficacy and safety in larger cohorts.

3043 Poster Session (Board #138), 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 significant challenge. We found a response signature with a specificity of 76% by random forests and Bayesian probit regression with non-local priors. We estimated classification performance via leave-one-out cross validation.
Methods: Patients treated with anti-PD-1 or anti-PD-L1 therapy alone and clinically documented response and toxicity were tested with a panel of over 150 germline microRNA 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 germline 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 98% by Random Forests, and a toxicity signature with a specificity of 76% by Random Forests.
Conclusions: We have shown that a new class of germline mutations disrupting microRNA regulatory networks can act as biomarkers of response and toxicity to anti-PD-1 and anti-PD-L1 therapy.
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: Amad Sanaei, 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.

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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 necropsitopes were identified. Approximately 10^9 neoantigen loaded DC vaccine and 10^15 bulk T cells composed of 10^7 neoantigen reactive CD8+ T cells were generated for personalized 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 customized 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.
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 (rGPC3+ HCC). First Author: Bo Zhao, 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 HCC. Safety and preliminary efficacy of a GPC3 CAR-T was evaluated in 13 Chinese patients (pts) with rGPC3+ HCC in a Phase I trial.

Methods: Pts between 18 and 70 yrs old with histopathologically confirmed rGPC3+ HCC. Child-Pugh scores B7, ECOG≤1, lymphocyte ≥3.0x10⁹, post-transduction positive T cells ≥30%, extrapolation by CD3/CD28 ≥50%, and without ascites and HCV infection were enrolled. Eligible pts undergo leukapheresis or whole blood collection, 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 receiving a total infusion of GPC3 CAR-T ranging from 0.92x10⁹ to 8.72x10⁹ 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 0.013x10⁹ to 1.64x10⁹ cells/kg. Except two non-evaluable pts, the best response for the rest 6 pts is 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 6.22x10⁹ cells/kg infusions following a LDC given around Day 150, remains stable for 571 days as of Feb 1, 2017. Conclusions: The Phase I trial shows GPC3 CAR-T is feasible and safe for Chinese pts with rGPC3+ HCC, and holds promising antitumor potential when LDC is applied along with GPC3 CAR-T. Clinical trial information: NCT02399250.

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 identity 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: Retrospective 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-Meier and Cox regression analysis was applied for survival analysis. The cutoff points 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, 4.42; 95%CI, 1.60–11.5; P < 0.01) and 28.5 vs. 7.7 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 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.

Durvalumab and tremelimumab in metastatic breast cancer (MBC): Immunotherapy and immunopharmacogenomic dynamics. First Author: César 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 antitumor activity in other cancer types. Immunopharmacogenomics characterizes immune-cancer cell interactions and may predict response. Methods: A single arm study was designed to determine the efficacy of durvalumab (PD-1 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 to meet criteria to proceed to the second stage. Notably, one pt with TNBC with 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.

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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 Medc Int 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 Wnt-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 BrafV600E-Pten−/− model, the genetic silencing of melanoma-derived Wnt5a potently enhances infiltrating CD8+ T cell effect function and promotes responses to anti-PD-1 Ab therapy. [Iparacetip (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/II 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 preclinical 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 a syngeneic murine autochthonous BrafV600E-Pten−/− melanoma model. **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 BrafV600E-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.

**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 tumor 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 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 metastatic tumor CI (0.1-1.7%). 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 2/3 (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.

**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 (CDSTI); 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 systemic inflammatory response (SIR) score 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 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 metastatic tumor CI (0.1-1.7%). 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 2/3 (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.

**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 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 Pkdc3a, Braf, NFI, Nras, and Pten genes. Interestingly, cases with mutations in Smo, Ddr2, Fgfr1, Pdcd1, Fgfr2, and/or Met appear to be enriched in those with progression and a higher likelihood of responding to immunotherapy. Of the 13,349 cases that could benefit from combination therapy, 50.9% had Braf, Nfi, Gnar2, and/or Gnar41 mutations which can be targeted by Trametinib; 26.1% by Taselisib (targets Pik3ca mutations); and 19.8% by Afatinib (targets Erbb2 and/or Erbb3 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.

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Conclusions: This large pooled analysis confirms that avelumab has an ac-
ceptable safety profile in patients with advanced solid tumors and demon-
strated clinical activity. Updated results confirm previous findings that suggest higher ORR/DCR 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 on days 1, 8, and 15 every 28 days. AEs were experienced in all pts (diarrhea [20 pts, 90.9%] and rash [15 pts, 68.2%] were most common); related grade 3–4 AEs in 54.5% (diarrhea [three pts, 13.6%] and dermatitis acruminatum [two pts, 9.1%]) were most common; no related G5 AEs; related severe 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 melanoma (median duration of response was not reached); DCR was 75.0%; mPFS was 12.0 months (95% CI 2.6–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.

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3061 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 CDB+ 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 sequences for data from 29 patients in whom we had 3 or more serial samples. Thirty (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 at all available 017- 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 A randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab, a PD-L1 antibody, to a taxane-antihyperglycemic containing chemotherapy in triple negative breast cancer (TNBC). First Author: Sylvie 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 i.g. i.v. or placebo (pl) every 4 weeks (wks). Dpl monotherapy (0.75 i.g. i.v.) is given for the first 2 wks (window phase), followed by a biopsy and Dpl plus nab-paclitaxel (np) 125 mg/m² weekly for 12 wks, followed by Dpl 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 cT1-cT4a-d disease, centrally confirmed TNBC, and stILs status can be included. Primary objective is overall response rate (ORR) and pCR defined as clinical complete response in the breast and axillary nodes and pathological complete response in the breast and any axillary nodes and any visceral or non-visceral metastasis.

Conclusions: Atezo consolidation with 2 cycles of CP after CRT appears to be feasible and welltolerated 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 A to CRT followed by atezo-C consolidation is open for accrual. Clinical trial information: NCT02525757.

3063 Atezolizumab (A) + cobimetinib (C) + vemurafenib (V) in BRAFV600-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 BRAFV600-mutant mel can lead to both anticancer immune activation and direct tumor cell death. A, an anti–PD1 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 (flu-like) profile and promising antitumor activity in patients (pts) with untreated BRAFV600-mutant unresectable/metastatic melanoma (mel). Here we report on TCR receptor β chain sequencing data for 29 patients in whom we had 3 or more serial samples. Thirty (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 at all available 017- 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.

3064 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 PD-L1/PD-1 (atezo) and standard 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 CRT, or II) CRT + atezo (N = 20) or CRT + atezo (N = 30). The first 10, 20 and 30 pts will be included in safety interim analyses. SIA was performed. No pt interrupted D/pl, one nP and one EC. Treatment delay was observed in 9 pts (20%) in D/pl and in 2 (13.3%) in EC; dose was reduced in 1 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 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.
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 cytokine-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 increasingly validated as potential cancer therapeutics. We tested the hypotheses 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. 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 or difference in the primary endpoint of immune response to PA2024 between two arms. More pts responded 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 indoximod may be a potential strategy to improve treatment outcomes for CRPC.

3067 Poster Session (Board #162), Mon, 8:00 AM-11:30 AM

A phase 1 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-thrombocytosis (42%), rash (39%), fever (28%), leukenemia (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 PD-L1 expression in tumor biopsy (66% 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 patients with under-evaluated acral (20% ORR, 53% DCR) and mucosal (25% ORR, 50% DCR) melanomas. Clinical trial information: NCT02836795.
### 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 ($PS$) $>\leq 1$, albumin $<\leq$ 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 $<35g/L$, $LDH$ $>\leq$ 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:** 59y (range 20-86), 28%/72% of pts were ECOG PS 0/1, and 88% had at least 1 prior systemic therapy (range (0.5 = no discrimination, 1 = perfect discrimination) and Area Under the Curve (AUC).**

**OS**

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<th>C-index</th>
<th>AUC</th>
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<td>0.42</td>
<td>0.44</td>
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**Conclusion:** In this independent validation cohort, the PM-IPI prognosticated for $OS$ and 90DM and was associated with improved overall response rate ($ORR$) and progression free survival ($PFS$). Validation in a large independent cohort of pts is ongoing.

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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. PVR2L2 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-γ 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 95C tumors when combined with an anti-PD1 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.

Methods:

3075 Poster Session (Board #170), Mon, 8:00 AM-11:30 AM
Integrating resistance mechanisms to PD-1 blockade therapy with CRISPR. First Author: Davis Yuin 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-A2/02:01 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 (< 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 the JAK2-KO and B2M-KO sublines. The percentage of CD8+ T cells and reduction in IFN-gamma expression in CD8+ T cells increased 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 PD-L1 in tumors from patients (pt) with NSCLC, gastroesophageal (GE) and urothelial bladder carcinoma (UBC). First Author: Philip Martin, MedImmune/ASAzeneca, Gaithersburg, MD

Background: Tumors use multiple means of immune evasion, notably the programmed death-1 (PD1)/PD-L1 pathway. Anti-PD1/PD-L1 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/PD-L1 therapies. We evaluated expression of CD73 and PD-L1 and explored the association between CD73 and intratumoral (IT) CD8+ cells (TILs) to begin to understand their potential interplay in cancer.

Methods: Immunohistochemistry for PD-L1, CD73 and CD8 was conducted on tumors of non-squamous NSCLC (NSq) (n=42), GE (n=50), and UBC (n=50). PD-L1 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 PD-L1 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 PD-L1 high (+), but CD73 low (-) and another 25% (35/142) were CD73+ but PD-L1- (p=0.06, see table). This trend for mutually exclusive high expression of PD-L1/CD73 was strongest in GE (p<0.001). In the PD-L1+ group 76% (35/46) had high IE CD8+ TILs whereas in the CD73+ group only 35% (16/46) had high IE CD8+ TILs (p=0.0001 using a proportions test). In the PD-L1+CD73- pt subset 77% (27/35) were PD-L1+/CD73-, whereas in the CD73+ group only 35% (16/46) had high TILs (p=0.01). In the PD-L1+ group 76% (35/46) had high IE CD8+ TILs whereas in the CD73+ group only 35% (16/46) had high IE CD8+ TILs (p=0.0001 using a proportions test). In the PD-L1+CD73- pt subset 77% (27/35) were PD-L1+/CD73-. The identification of distinct pt subsets based on high PD-L1 and/or CD73 expression suggests that tumors have multiple mechanisms of immune evasion. Increased IE CD8+ TILs were associated with PD-L1 expression. The finding that PD-L1+/CD73- tumors have lower IE CD8+ TILs compared to PD-L1+ and PD-L1+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 PD-L1 and CD73.

3080 Poster Session (Board #175), Mon, 8:00 AM-11:30 AM

Characteristic 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: Immuno-oncology with checkpoint blockade was recently approved for patients with pretreatment 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-GRZB was significantly lower in HPV-negative compared to HPV-positive tumors (p = 0.002), suggesting 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 MUC154C that is preferentially expressed with exquisite specificity to colorectal 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 I/II clinical trial of adult pts with refractory mCRC.

Methods: - 20% expression of tumor suppressive CD39/CD73/adenosine pathway might play a role in pts who do not benefit from anti-PD1/PD-L1 therapies. We evaluated expression of CD73 and PD-L1 and explored the association between CD73 and intratumoral (IT) CD8+ cells (TILs) to begin to understand their potential interplay in cancer.

Results: Across all tumors, 25% (35/142) were PD-L1 high (+), but CD73 low (-) and another 25% (35/142) were CD73+ but PD-L1- (p=0.06, see table). This trend for mutually exclusive high expression of PD-L1/CD73 was strongest in GE (p<0.001). In the PD-L1+ group 76% (35/46) had high IE CD8+ TILs whereas in the CD73+ group only 35% (16/46) had high IE CD8+ TILs (p=0.0001 using a proportions test). In the PD-L1+CD73- pt subset 77% (27/35) were PD-L1+/CD73-, whereas in the CD73+ group only 35% (16/46) had high TILs (p=0.01). In the PD-L1+ group 76% (35/46) had high IE CD8+ TILs whereas in the CD73+ group only 35% (16/46) had high IE CD8+ TILs (p=0.0001 using a proportions test). In the PD-L1+CD73- pt subset 77% (27/35) were PD-L1+/CD73-. The identification of distinct pt subsets based on high PD-L1 and/or CD73 expression suggests that tumors have multiple mechanisms of immune evasion. Increased IE CD8+ TILs were associated with PD-L1 expression. The finding that PD-L1+/CD73- tumors have lower IE CD8+ TILs compared to PD-L1+ and PD-L1+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 PD-L1 and CD73.

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 Marañon, Madrid, Spain

Background: BO-112 is a double stranded synthetic RNA, formulated with the cationic polymer polyethylenimine 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 enhanced 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 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.
Background: PG545 (pixatimod, pINN) is a novel immunomodulatory agent that stimulates dendritic cells (DC) via Toll-Like Receptor-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 0-2) 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 (plasma cytokinetics), and plasma cytokines/chemokines. Results: The study recruited 23 subjects across four cohorts (25, 50, 100 & 150 mg). Three dose limiting toxicities (DLTs) - (hypertension, epistaxis) - 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 REDIST 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 (AUC0-∞) was proportional up to 100 mg and mean half-life was 24 hours. At 50 and 100 mg dose levels, two subgroups of 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 chemotherapies, support the development of PG545 in combination clinical trials. Clinical trial information: NCT02042781.

**Abstracts evaluated safety, antitumor activity based on RECIST (1.1) criteria, was determination of the maximum tolerated dose (MTD). Secondary objectives evaluated safety, antitumor activity based on RECIST (1.1) criteria, PK and PD (plasma cytokinetics), and plasma cytokines/chemokines. Results:** The study recruited 23 subjects across four cohorts (25, 50, 100 & 150 mg). Three dose limiting toxicities (DLTs) - (hypertension, epistaxis) - 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 REDIST 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 (AUC0-∞) was proportional up to 100 mg and mean half-life was 24 hours. At 50 and 100 mg dose levels, two subgroups of 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 chemotherapies, support the development of PG545 in combination clinical trials. Clinical trial information: NCT02042781.

**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) as an autologous vaccine. 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. Adjuvant injections of LTX-315 into a single accessible tumour over 6 weeks. Ad- ditional injections could be administered thereafter every 2 weeks. Biopsies of injected tumors were taken at baseline and at each cycle of treatment. Results: 25 melanoma pts who had stable disease at 50 and 100 mg reached 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 chemotherapies, support the development of PG545 in combination clinical trials. Clinical trial information: NCT02042781.
The RP2D of INVAC-1 is therefore a monthly ID injection of 800 pts, 400 the per-protocol 3-month duration, up to nine months for 2 pts. IFN-g disease and clinical benefit. For 10 pts, the treatment was extended beyond defined. The most common treatment-related adverse events were grade 1 or limiting toxicities or treatment related SAEs have been reported; no MTD was m

hematologic malignancies, either as monotherapy or in combination with results encourage a future evaluation of INVAC-1 is solid tumors, as well as in clinical models, INVAC-1 triggered Th1-polarized hTERT-specific CD8+ and shared tumor antigen expressed in more than 85% of human tumors. Tel-

metastatic patients receiving 10x106 viable DCs per dose or higher, 7 of 19

activity. 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: 12 pts experienced dose 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: NCT02301754.

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A phase I study of the bispecific antibody T-cell engager GBR 1302 in subjects with HER2-positive cancers. First Author: Martin Wernke, Universitaetsklinikum 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 OX3-specific domain of the molecule. Preclinically, GBR 1302 has demonstrated potent killing of HER2-positive human cancer cells (HER2 + or + 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 + 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 (NCT03018405). The effects of GBR 1302 on the adaptive immune system will also be studied at the cellular and serological levels in translational research. Clinical trial information: NCT02829372.

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**TPS3093** Poster Session (Board #187a), Mon, 8:00 AM-11:30 AM

A NKGD2-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, Celldyn, 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 NKGD2 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-molecules. We have developed a potent killing of ovarian cancer. Clinical trial information: NCT 02948426.

**Methods:** Patients with recurrent or refractory ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with no standard treatment are available. Intravenous GBR 1302 is given every 2 weeks (NCT03018405). The effects of GBR 1302 on the adaptive immune system will also be studied at the cellular and serological levels in translational research. Clinical trial information: NCT02829372.

**Conclusions:** This novel and open-label CAR-T therapy in a multinational phase I dose escalation and expansion study targeting multiple solid and hematologic tumor types will be administered intraperitoneally, is likely that the administration of IFNs and monocytic in preclinical models, providing a long and durable response. Additionally, monocytic IFNα and IFNβ 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 monocytic inpreclinical models will create a strong anti-tumor environment and can overcome the immunosuppressive environment of epithelial ovarian cancer. We hypothesize that the monocytic CAR-T therapy will be tolerable to women with relapsed ovarian cancer. Methods: Part 3 of a phase I single arm study to determine the maximum tolerated dose of intraperitoneal monocytic CAR-T cells 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 monocytic CAR-T cells 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.

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A phase 1/2 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 × 10^6 CD30.CAR-Ts/m² 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 1/2 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/m² 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 × 10^6 CD30.CAR-Ts/m². 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 × 10^6/m². 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. Clinical trial information: NCT02690545.

A pilot study of NY-ESO-1 \(^{1259}\) T cells in subjects with advanced myxoid/diffuse cell liposarcoma (NCT02992743). First Author: Sandra P. D’Angelo, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Myxoid/diffuse 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 \(^{1259}\) T cells recognizing NY-ESO-1 derived peptide complexed with HLA-A*02. Inclusion criteria for patients (pt) enrolled in this 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, progression free survival, overall survival), safety, and persistence of CAR-Ts. Patients are screened (NCT02636855) to identify those who have the relevant HLA-A*02 alleles and NY-ESO-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 (NCT02386855) 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 IIb 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.

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-A*02 and/or *02:06 positive and have inoperable or metastatic (advanced) urothelial cancer, melanoma, or uterine tumors (NCT02998064). 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 \(^{796}\) T cells directed towards a MAGE-A10 peptide expressed on tumors in the context of HLA-A*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 (NCT02636855) to identify those who have the relevant HLA-A*02 alleles and NY-ESO-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 (NCT02386855) 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 IIb 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.

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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 250 pts with advanced solid tumors or lymphomas on 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 ≥ 18 years, ECOG ≤ 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.

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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 subjects 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:E1160.) (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 long-term memory, regulates regulatory T cell suppression and provides survival benefit in animal models of tumor challenge (Linck SN, et al., Front Oncol. 2015;5:34). MEDI0562 is an investigational, humanized IgG1 anti-OX40 mAb that triggers OX40 signaling. Co-administration 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-1 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 AE s, serious AE s, 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.
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 sarcomas 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 duallettes 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 Stage IIIB disease. Though not required to substantiate, there is a significant 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 tumors following treatment with pembrolizumab. Enrollment is ongoing. Clinical trial information: NCT02721732.

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**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. PbtXs are fully recombinant antibody prodrugs designed to be converted to active antibodies by tumor-associated proteases that are highly expressed in malignant tissue; the PbtX remains largely inactive in normal tissue. In preclinical tumor models, a Pd-L1-directed PbtX provided comparable anti-tumor efficacy to its parental anti-PDLL antibody, but displayed reduced autoimmunity in a model of Type 1 diabetes. Based on these preclinical data, CX-072 has the potential to enable combination therapies that are otherwise poorly tolerated. This Phase I/II study (PROCLAIM-001 (PProBody 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-L1 inhibitor, but did not discontinue treatment due to toxicity. Part C: checkpoint inhibitor-naive 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 cossackievirus A21 and pembrolizumab in advanced cancer patients.**

First Author: Hardev S. Pandha, University of Surrey, Surrey, United Kingdom

**Background:** Cossackievirus A21 (CVA21, CAVATAK) is a naturally occurring ICAM-1 targeted oncolytic immunotherapeutic virus. Pembrolizumab is a human anti-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 1b 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 10^6 TCID_50 in Cohort 2 (n = 3) at a dose of 3 x 10^6 TCID_50 and in Cohort 3 (n = 80) at a dose of 1 x 10^7 TCID_50 on study days 1,3,5,8,29, and Q3W for 6 additional injections. 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 complete response (CR), partial response (PR), disease progression (PD), or withdrawal. 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 autoimmune/ 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 (SIRPa) 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 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 inhibits the CD47-SIRPa signal and has been shown to enhance benefit in the clinic. The combination of i.v. CVA21+pembrolizumab may translate to a potential enhanced benefit in the clinic. Methods: Part A is a single arm 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/RPD2 or “active dose” is determined, patients with specific solid tumors and high CD47 expression will be enrolled in Part B. In Part B, 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 $\geq$200 mg QD (Bendell JC et al. Mol Cancer Ther, 2013;12:A252). Preclinical data supports combining a P-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 pembrolizumab in patients with selected advanced solid tumors. 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 autoimmune/ immunosuppression. Clinical trial information: NCT02280371.

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prised of IL-2R

circularly permuted interleukin-2 (IL-2) and IL-2 Receptor (IL-2R)  

**Background:** ALKS 4230 is an engineered fusion protein comprised of a Vaishampayan, Wayne State University, Detroit, MI  

effector T cells, in patients with advanced solid tumors.  

**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:** Ulika 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-2Rβγ. 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 (Treg) 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 escalation will be halted 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 Treg 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 (TDC) is a proven therapy strategy in cancer. ERY974 is a humanized IgG4 bispecific antibody designed to simultaneously bind to cytotoxic T-cell GPC3 receptors and GPC3 (a glycoprotein expressed on cell surface of several tumors) to elicit T-cell activation and TDC. 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 1st and 2nd 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 ≥2 G2 CRS is again observed, then at all subsequent doses the 1st dose of ERY974 is fixed at the last dose level when < G2 CRS was not seen, DE proceeds with the 2nd dose. ATD commences with n = 1, increasing to n = 3 once drug-related ≥2 G2 toxicity is seen. mCRM starts after 1st dose limiting toxicity (DLT), with the modification 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 ≥3 months. Patients with > 1cm or > 1 brain metastasis, current/previous intestinal 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/Inducible T cell Co-Stimulator (ICOS), a member of the CD28/  

**Methods:** INDUCE-1 is a first-in-human phase 1 study evaluating a human IgG1 antibody, administered as an intravenous 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 will be evaluated in an expansion cohort. 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. Efficacy measures are 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 at least one of the following tumor types: non-small cell lung cancer, (c) ductal or lobular breast cancer, (d) serous non-small cell lung cancer, (c) ductal or lobular breast cancer, (d) serous carcinoma of the ovary, uterine adenexa, (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 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.

**TPS3114 Poster Session** (Board #197b), Mon, 8:00 AM-11:30 AM  

A phase 1 study of the safety and immunogenicity of a multipetide 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:** 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 at least one of the following tumor types: (a) head and neck squamous cell cancer, (b) other immunotherapies such as pembrolizumab. The unique mechanistic profile of an ICOS agonist antibody, administered alone and in combination with pembrolizumab in patients with advanced 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 will be evaluated in an expansion cohort. 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. 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; DL4 enrollment is ongoing. Study is funded by GlaxoSmithKline and is in collaboration with Merck & Co., Inc. Clinical trial information: NCT02723955.

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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 PD-L1 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.

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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.
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, Hôpital 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, 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 52.0 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-month 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 6.62/28.5/7.9/5.9% in 3M and 33.4/1.3/25.3/6% 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%. 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 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 1.09–1.35, 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 at 6 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 FARM581111.

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 Lesen, 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 toxic effects 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 OxMg or Xelox (physician/patient choice) in Stage III/II colorectal cancer, non-inferior 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% one-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: 6086 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 OxMg for 1016 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 OxMg (test for heterogeneity, p = 0.059). Results will be presented in line with the international IDEA project that will also be presented at ASCO 2017. Clinical trial information: IRCTN59757862.

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 1-st line FOLFOX or FOLFIRI in All RAS wild type (wt) mCRC pts. There was a significant 1° site by biologic interaction (P int: OS = 0.008, PFS = 0.001) favoring 1°. Analyses of 1° tumors beyond All RAS wt (44%) included 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 (L - and R - sided T 1°s) available was as follows: KRAS- 291, NRAS-393, BRAF-393, MSI-378, CMS-533. Ls Rs M&O. 32.9 ±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 these all 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 impact the influence of sidedness. Support: U10CA188021, U10CA189082. Ely Lily and Co, Genentech/Roche, Pfizer, Sanofi. Clinical trial information: NCT002655850.

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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 mut (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 chemotheraphy, 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 1.32, 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 vs. Cet arm (p = 0.041); in pts no 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 Bev arm no difference is observed in larger datasets (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 should be tested in larger datasets. Updated results from more screened patients will be presented.

Median OS 95% CI (months) HRlog (95% CI)
BRAF mut (N=515)
Bev 17.4 (12.3,32.6) 0.49 (0.25,0.97) REF
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) REF
Cet 30.1 (25.6,34.6) REF
MSI-H (N=21)
Bev 30.0 (10.9, NE) 0.13 (0.04,0.46) REF
Cet 11.2 (9.4,24.6) REF
MSI-S (N=320)
Bev 32.6 (26.3,36.0) 0.86 (0.64,1.15) REF
Cet 30.1 (27.4,32.2) REF

Support: U10CA180821, U10CA180882, Gentencht, Eli Lilly, Sanofi.

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 overall survival. The SUNSHINE trial is a phase II trial 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 chemotherapy, no metastatic disease, and 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=0.02. 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 chemotherapy-naïve mCRC patients (performance status 0/1) with liver metastases not suitable for curative resection/ablation. Arm A was oxaliplatin-based chemotherapy (mFOLFOX6/ OxMgd = investigator-chosen biologically targeted). Arm B was 2 cycle IV xenograft + single treatment SIRT with cycle 1/2 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 in HR (1.04, 95% CI 0.90-1.2, p = 0.690) or PFS (HR 0.91, 95% CI 0.79-1.02, p = 0.082) between Arms. Objective response rate (ORR) was 29% vs. 13% (p = 0.033). Time to progression was 7.1 months in Arm A vs. 6.4 months in Arm B (HR 0.78, 95% CI 0.66-0.93, p = 0.003). Time to disease progression was 7.9 months in Arm A vs. 6.4 months in Arm B (HR 0.78, 95% CI 0.66-0.93, p = 0.003). In health status questionnaires, EQ-5D utility scores were not significantly different between Arms (HR 0.98, 95% CI 0.96-1.01, p = 0.450). Conclusions: 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

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-mutant (mut) mutations have poor outcomes with standard care chemotheraphy and rarely respond to the BRAF inhibitor vemurafenib. In preclinical models, blockade of BRAFV600 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 BRAFV600 mut and extended RAD wild-type mCRC were randomized to irinotecan (180 mg/m² IV every 14 days) and cetuximab (500 mg/m² 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 (C) 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) mos. Response rate was 16% vs 4% (P = 0.08), with disease control rate of 67% vs 22% (P = 0.08) with vemurafenib added to the VIC triplet (vemurafenib, cetuximab and 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 (15% 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 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 BRAFV600 mut mCRC, and support VIC as a potential new treatment option in this molecular subset. Clinical trial information: NCT02164916.
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 #211). 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 violations with several OS and clinical features according to K-ras status and CMS 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 CCMS classification with 23 of 431 failures showing a shorter OS in CMS4, although there were no significant differences across CMS groups, although there are significant and clinically meaningful OS benefits 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.

3510 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM
Consortial 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, 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), DFS (p = 0.001) and OS (p < 0.001). For data on CMS and treatment efficacy in the RAS wt population see the clinical routine.

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 CMS showing the best HR.

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 Leitz, Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, United States

Background: CALGB 80405 was a randomized Ph3 trial comparing 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: We validated molecular CC subtyping predictors for both CMS and CCMS classifications on PETACC-8 FFPE samples. The prognostic value of CMS and CCMS 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.
A phase III trial (ZJ80009): 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 Chemical 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-fluorouracil plus oxaliplatin more than 1 month of the last-dose enrolled in study. Pts were randomly assigned on a 2:1:1 ratio to receive CMAB009 (initial 400mg/m² on day 1, and then 250 mg/m² weekly) plus irinotecan (180mg/m², every 2 weeks) (A arm) or irinotecan alone (B arm). B arm pts could switch to CMAB009 sequential treatment (C arm) on disease progression. The primary end point was overall response rate (ORR). The secondary endpoints were PFS, OS, DOR, and ORR (NCT01550055). Results: From May 2009 to December 2012, 512 pts were assigned from 38 sites. Efficacy evaluation was performed every 8 weeks. DCR was 63.5% (331/512). In B arm, the ORR was 21.0% (107/512) vs 10.9% (23/210) in A arm and 9.5% (10/104) in C arm (p<0.0001). A survival analysis was performed with the last observation carried forward. Median PFS was significantly longer in A arm than in B arm (169 days vs 95 days, p<0.00001). A 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). The most frequent AE was neutropenia and fatigue. Adding CMAB009 to irinotecan increased the risk of Grade 3/4 nausea (6.5% vs 5.5%, p<0.001) and paronychia (9.8% vs 5.0%, 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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_adj= 0.03) for DFS and 0.43 (95% CI, 0.25 to 0.74; P_adj= 0.01) for overall survival (OS). On subgroup analysis, the significant association was confined to the TNT cohort: HR = 0.54 (95% CI, 0.34 to 0.85; P_adj= 0.04) for DFS and HR = 0.47 (95% CI, 0.27 to 0.82; P_adj= 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: U101CA180821, U101CA180882, Pfizer. Clinical trial information: NCT00038335.

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 (chemoRT). Of these, 120 pts received TNT (preoperative 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 < 0.005 and p < 0.001, 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 a cCR (p=0.001), N downstaging (p < 0.005), a cCR (p = 0.005), or a pCR (p < 0.005). 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.

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 che- moradiotherapy (COREAN) trial. Methods: COREAN 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 = 0.27; 7-year local recurrence: 3.3% [laparoscopic] vs 4.7% [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 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.

Colorectal cancer (CRC) patients surveyed by 18FDG PET-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-year follow-up period. Every 3 months, multidisciplinary committee decided about recurrence based on clinical and/or imaging. If recurrence was confirmed (when relevant), or chemotherapy alone (unresectable 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-Rank 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 = 0.32). Similar results were observed in multivariate analysis (Cox models) adjusted for stage and tumor differentiation (HR = 1.33, 95% CI: 0.82-2.19, P = 0.27). Period until the unresectable recurrence was significantly shorter in Interventional (median = 7; IQR: 3.8-28.19) 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) costs per euro/patient was higher in the PET-Scan (9385; 11658) than in control group (9027; 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: NCT00624260.
The potential of circulating tumor DNA (ctDNA) to guide adjuvant chemotherapy decision making in locally advanced rectal cancer (LARC).

First Author: Michael J. Overman, The University of Texas MD Anderson Cancer Center, Houston, TX

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+) is 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-center study in pts with LARC (T3-4 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 and demonstrated a median follow up of 22 months. Of the 122 pts who had detectable ctDNA prior to therapy, 34 pts (28%) indicated that under anti-survival. A subset of patients demonstrated an overall decrease in tumor burden and/or disease-free survival. A single individual could have both net gain and/or net loss of mutations (ordered by frequency). New mutations were noted both inside and outside the EGFR pathway. EGFR pathway genes with significant net gain or loss of mutation were: EGFR (HR 4.2, p = 0.001), KRAS (HR 0.001; no chemo: HR 16, p < 0.001), BRAF (HR 0.001), NRAS (HR 0.001) 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 of 15 genes applied in patients with advanced cancer pts with a high theoretical sensitivity (96%) for CRC. Minimal unique molecular coverage for this study is 9000 for ctDNA inputs ranging from 10–150 ng (media input prep = 27 ng, median input postop = 49 ng) with 120,000X sequencing depth on an IIlumina HiSeq2500.

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Conclusions: 0.39; p, analysis (90 MABp1 vs 49 Placebo). Median OS of those achieving the continued study prior to the week 8 assessment due to disease progression, 57 patients (38 MABp1 [18%] and 19 placebo [19%]) dis-

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Conclusions: 

Conventional histology (83% vs 63%) and moderate differentiation (82% vs 61%) alterations predicted for survival, but primary site did not (HR = 0.74, p = 0.03), BRAF (HR = 3.7, p = 0.0001). The added value of SIRT is not well established. 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. 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 FOLFOLFOX chemotherapy+bevacizumab (bev) (CT) vs CT+SiRT in the phase III SIRFLX trial were reviewed by 3 expert HPB surgeons (from a panel of 15) for resectability of LM. Reviewers were blinded to each other and to all clinical information incl. 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 compared with 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 FOLFOLX+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.

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 consecutively treated MSS mCRCs. Primary tumor site was divided into right-sided for cecum to distal transverse colon (n = 242), left-sided for splenic flexure to cecum to distal transverse colon (n = 242), for growth of CRC, respectively. Results of 242 right-sided mCRCs from our institution (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. We assessed Early LCR by the ARCAD database.

Results: The Early LCR correlated 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.

Conclusions: 

Conclusions: The Early LCR correlated 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.

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 — biological: 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-patient 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 association between kinase (RTK) LCR and overall survival (OS). Adjusted hazard ratios (HRadj) 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 (EGFi), respectively. LCR heterogeneity is the highest among pts received VEGFi but lowest among pts received EGFi (Table). Overall, higher heterogeneity is associated with worst OS (HRadj1.22, 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. This magnitude varies across treatment approaches, and was associated with survival. Overall, this preliminary result reveals the great potentials to define novel response endpoint and refine treatment decision-making by incorporating heterogeneities in lesion changes.

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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 (55%) and frequent peritoneal carcinosis (43%). Lynch syndrome was found in 34% of cases and 36% of tumors had a BRAFV600E mutation. Median OS was 20.6 months. A low risk Kohen’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 SFU-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%, 3% and 36% for SFU-based, oxaliplatin-based and irinotecan-based chemotherapies, respectively (p = 0.02). A trend for a longer PFS (3,3, 5, 10 and 12 months, respectively, p = 0.06) and OS (17,7, 21, 11 and 34,2 months, respectively, p = 0.05) was also observed for oxaliplatin-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 chemotherapy, especially to SFU-based chemotherapy. Efficacy of irinotecan and bevacizumab should be evaluated in a prospective trial in combination with immune checkpoint inhibitors.

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Regorafenib (REG) versus trifluridine/tipiracil (TAS-102) as salvage-line treatment in patients with metastatic colorectal cancer refractory to standard chemotherapies (REGOTAS): A propensity score analysis from a JSSCR 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 (JSSCR). 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) were included in the propensity analysis 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/FOLFOLX06 for treatment of TRIBE and MOMA studies by GONO group. Following a 24-week treatment with furamitrex glutathione and improve outcome in patients with CRC irrespective of tumor localization. The aim of the present study was to focus on treatment arms showed a better PFS and OS for REG mono treatment compared with TAS-102. The most clinically relevant result was an improvement of median progression free survival (PFS) and overall survival (OS) from start of maintenance according to LPT in FOLFOXIRI plus bev, 429 progressed. 303 (70.6%) pts received a 2nd line tx: 93 FOLFOXIRI +/- bev (Group A), 119 FOLFOXEXLOL or FOLIRI +/- bev (Group B) and 91 other tx (Group C), including an anti-EGFR mAb in 60 cases. No difference in clinical activity was seen in patients with untreated advanced CRC including those with proficient MMR. Clinical trial information: NCT02375672.

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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 CHARITA-AIO 0209 trial. First Author: Julia Quinde, Department of Oncology, Hematology and Bone Marrow Transplantation with Section Pneumology, Hubertus Wald-Tumor-Zentrum (UZH), University Hospital Hamburg-Eppendorf (UKE), Hamburg, Germany

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 QLC-C30, QLC-CR29 and QLC-IPN20. 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 chi² tests. Results: For HRQOL analysis, 237 patients were eligible (arm A: 118; arm B: 119). Compliance was 95.4% at baseline, 72.6% at week 6 of treatment (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 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 and B; p = 0.461). Conclusion: 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.

Efficacy of bevacizumab in second-line versus first-line treatment of metastatic colorectal cancer: Results from a new methodological approach based on the ITAcs strategy trial. First Author: Elisabetta Petracchi, Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRGCS, 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 treatment line in a study sometimes end up analyzing data in a non-systematic way. Methods: Data from the ITAcs 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 options: chemotherapy (CT) plus bevacizumab (B) 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 addition 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 addition 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 ITAcs 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: NCT01387422.

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 (≥75 years). However 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. The purpose was 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 12 months in pts aged ≥75 years old with mCRC. The main endpoint is 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 Folflox (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 19.2 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 derive benefit from 1st line bev plus chemotherapy in daily practice in this population. The safety profile is acceptable. Clinical trial information: NCT01555762.
Concordance of DNA mismatch repair deficient (dMMR)/microsatellite instability (MSI) assessment by local and central testing in patients with metastatic CRC who progressed on or were intolerant of treatment is appropriate for identifying the dMMR/MSI-H pts who may benefit from nivolumab (nivo) monotherapy. Clinical trial information: NCT02060188.

Methods: MMR/MSI status was assessed locally on archival tumor using IHC/PCR testing 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 (MSI), 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 who progressed on or were intolerant of ≥1 prior line of therapy received nivolumab 3 mg/kg Q2W.

Results: 354 malignant CRC pts were identified centrally as dMMR but locally as MSS (Table). In this subgroup, median OS was 15.2 months in pts treated with nivo, compared to 8.3 months in those treated with treatment cycle rechallenge (HR 0.66, 95% CI 0.51, 0.87). Pts with MSS centrally confirmed as dMMR at baseline had a median OS of 12.6 months, while pts with MSS confirmed locally at baseline had a median OS of 11.0 months (HR 1.14, 95% CI 0.88, 1.47).

Conclusions: Results of local and central testing with respect to MMR/MSI status and clinical outcomes in the CheckMate 142 study, were centralized and confirmed by central testing. Concordance of dMMR/MSI-H was high between local and central testing. 14 pts had a central test that did not match local test results. Of the 14 pts, 3 were centrally confirmed as MSI-H. The concordance between local and central testing in all patients is currently being analyzed. Results of the phase II study of nivolumab as a first-line treatment in patients with metastatic colorectal cancer are currently being analyzed.
Prolonged (PI) vs short-term irinotecan (STI) administration: The Martha phase III study in the first-line setting of metastatic colorectal cancer (mCRC) patients (pts). First Author: Vincenzo Fornica, Tor Vergata University, Rome, Italy.

Background: FOLFIRI+bevacizumab (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 FOLFIRI+B for 6 months (m) followed by maintenance B monotherapy up to 12m (PI arm) vs FOLFIRI+B for 3 m followed by capecitabine+B for further 3 m followed by monotherapy up to 12m (STI arm).

Methods: Chemotherapy-naïve pts with histologically confirmed mCRC and measurable disease were deemed eligible and randomised to PI or STI arm in a 1:1 ratio. Co-primary endpoints were progression free survival (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 observed. 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-benefiting status (OR 2.3, p = 0.009; i.e. a 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 g/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 m, respectively, HR 0.64, p = 0.004). 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 chemoresistant and aggressive disease with the prolonged use of irinotecan.

Clinical trial information: EudraCT 2008-004890-17.

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Gastrointestinal (Colorectal) Cancer

3552 Poster Session (Board #175), 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 (~ 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 ≥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 arm of > 6 months OS benefit from tumor debulking will be achieved. Clinical trial information: NCT01792934.

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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: 5,168 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), 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 FOLFIRI 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.

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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 chemo-refractory 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 (ṣ070yo). 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 + trivatan (BRIV) with CETUX + placebo. Key eligibility criteria were similar between each trial. Patients were dichotomized by age (ṣ070yo/ < 70yo) for comparisons. Outcomes included overall survival (OS), progression free survival (PFS), quality of life (QoL), adverse events (AEs). Results: 5,076 pts were included; 63% were male; median age was 62. See Table for treatment details. Pts included in analysis. Multivariate analysis with Cox regression controlled for additional variables. Results: 980 patients were included in this analysis. 257 (26.2%) were ọ70yo 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). Comparing 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 (5.9m vs 7.6m, p = 0.02); however, grade 3/4 AEs were higher in younger patients treated with 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.
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 (retropertioneal 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 to colorectal cancer received trimodality therapy defined as chemotherapy, abdominopelvic lymphadenectomy and intraoperative radiotherapy (IORT). Infusional 5-FU

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: 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 endpoint was clinical benefit rate (CR, PR and SD). A number of pharmacodynamics correlates were assessed including serum cDNA, 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 was 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 (150%) or (2%) 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.

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 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 ≥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 1-38), with 15 (68%) pts receiving ≥15 DCR at first assessment. AeS (all grades) were 68%, with 5% CR, 47% PR and 16% SD. Median follow-up from diagnosis was 29 months (95% CI 18-42). Median OS was 51 months (95% CI 85-103); 12-month OS was 89%. Median OS from PD-1 therapy was 16.1 months (95% CI 16-19); 12-month OS from PD-1 therapy was 70%. Median PFS was 80.8 months (95% CI 5-59); 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 benefits in dMMR mCRC, even in heavily pretreated pts.
Gastrointestinal (Colorectal) Cancer

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: Thiwuvarudeth 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 subgroups 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 datasets, 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, Microsatellite 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 liver, bone and lung mets (RR=1.7, 2.0). MSI status was not associated with site of mets though liver only mets was less frequent in MSI high mets. 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 |
--- | --- | --- |
Overall | 15 | 25 |
Liver only | 20 | 30 |
Lung only | 29 | 39 |
Brain | 6 | 6 |
Bone | 12 | 17 |
Peritoneum | 12 | 17 |

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 Beggoff, University of Vienna, Vienna, Austria

Background: Brain 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 histo- logical 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) 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 Karnofsky 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
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, Korea

Background: Activating RAS mutation is a negative predictor of anti-EGFR therapy. In the final analysis of 21001007, the phase 3 trial of pmab vs BSC alone in chemorefractory mCRC, the addition of pmab resulted in improved OS and PFS. Methods: Anti-EGFR naive pts with WT RAS exon 2 mCRC were randomized 1:1 to pmab + BSC or BSC. Pts were further evaluated for RAS status, and DpR (percent tumor shrinkage at nadir or progression) and ETS (<< OS vs >= 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 RAS exon 2 mCRC, 270 were WT RAS (142 pmab + BSC; 128 BSC alone). In the pmab + BSC arm, 65.9% and 38.2% of pts had >=20% and >20% ETS, respectively, and median OS (21.7) was 16.9% (90%, 37.5%). OS was improved in pts with higher ETS (< > 20%) compared with lower ETS (< < 20%) (Table). Conclusions: This post-hoc analysis, pmab monotherapy provided any ETS benefit (>20%) 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 in- formation: NCT01412907.

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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 AE, 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 ± 9.7 years, 70.5% were male, and 83.8% received first line oxaliplatin based combination chemotherapy. AEs occurred in 99.1% 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 ± 2.7. The most common toxicities included diarrhea, neuropathy and fatigue. None of the toxicity scores 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, Hospital Lariboisiere AP-HP, Service de Chirurgie Digestive 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). Conclusions: Rate of adjuvant chemotherapy after CRS/HIPEC was comparable between the two groups (70.5% vs. 72.4%, p = 0.64). The median duration of follow-up had a part of worst OS and DFS comparing non-MM and MM patients. OS and DFS may be increased by utilizing cumulative toxicity scores to better guide adjuvant therapy management.

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 interin analysis from the prospective, observational CORRELATE study. First Author: Michel Ducruex, 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 randomised, 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 patients who progressed to chemotherapy. OS and PFS were compared between patients with L vs R tumors. Results were compared with the results of a similar study conducted 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 prior resection (40% vs 70%). Prior to 24 months of survival, 91.7%, 71.6% and 51.6% respectively in the patients with unselectable disease, and 98.1%, 92.2% and 88.8% in patients who were able to be resected with curative intent. Conclusions: This study suggests that patients who survive 24 months with stage IV colorectal cancer have an excellent prognosis. For patients who are unselectable 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.

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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 vs 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 were 34.2 months, and 28.2 months respectively (p = 0.12) from first line therapy. Median OS for patients who underwent second and subsequent anti-EGFR as subsequent therapy was 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 chemo-therapy or as a single agent. Updated results from commencement of anti-EGFR therapy will give further insights and will be presented at the meeting.

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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) versus non-responding tumours (nRT). These were co-cultured with TILs to organoid ratios of 1:1, 5:1 and 10:1 for 48 hrs and TIL 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 tumour organoid conform CD8+e 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.

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 benefit from robotic procedure need investigation. 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). Patients were randomized into two groups, robotic group (n=58) and open group (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 PODS, and (lower liver-related tumor size 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: NCT025262978.

Background: A limited understanding of the immune microenvironment of mismatch repair-proficient metastatic colorectal cancer (mCRC) impedes efforts to develop effective immunotherapeutic 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 metastectomy (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 recurring. Among immune related genes CXCL5, IFN4, IL6R, TNF, CTLA4, ICOS, and AFRF1 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 = 0.000). 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%, 3%, and 2.6% respectively. Conclusions: TAM 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.
Prospective study of biomarkers in squamous cell carcinoma of the anal canal (SCCAC) and their influence on treatment outcomes: Final results.

**Background:** While chemoradiation (CRT) is a curative treatment for SCCAC, many patients (pts) present primary resistance. As a rare tumor, there are no predictors of response in this setting remain unknown. **Methods:** Prospective cohort study aimed to evaluate predictive biomarkers (Ki-67, PD-L1, Human papillomavirus (HPV), HPV status and mutations in tumor DNA) associated with complete response (CR) following standard CRT for localized SCCAC. Eligible pts had T2-4N0-3M0 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 PapSureCheck Test. Ki-67 and PD-L1 were evaluated by immunohistochemistry. Results: 78 pts were recruited from Jan2011 to Dec2015, 75 were evaluable for response. Median age 57 years; 49 (65%) were stage III, and 9 (12%) were HI+. 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% (IQR 190%) per patient. Clinical stage, histotype, 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, ECOG ≥ 1 were 4.7 more likely to achieve CR (HR 0.19, 95% CI 0.10-0.36, p = 0.001), CTNNB1 mutation (HR 2.14, 95% CI 1.04-4.41, p = 0.039), and higher density of CD3+ IM had the strongest association with DFS, and was significantly associated with poor prognosis. Pts with HPV+ tumors were 3.2 more likely to achieve CR (HR 0.32, 95% CI 0.16-0.63, p = 0.003). Conclusions: SCCAC is a hi-risk tumor with poor outcomes, but there are different patterns among the sites. Combinations of immune markers and Immunoscore may help predict outcomes but need validation in larger clinical trials.

**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 right-sided colon tumors (LT) have better survival and respond differently to biologics compared to patients with left-sided colon tumors (RT), likely due to molecular differences. We sought to examine these differences. **Methods:** Primary colorectal tumors (n = 1730) with origins clearly defined as LC (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, LT 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 = 0.03) 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%; p = 0.04) mutations. There was no difference in the rate of MSI-high tumors (9.5% vs 9.7%; p = 0.6), or CRC had a higher rate of KRAS mutation (50% vs 42%; p = 0.04). There were no differences between LT and RC, or 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). 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 a genetic profile that is 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.

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**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 prioritization 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-occurring 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<sup>mut</sup>/TP53<sup>mut</sup> and TP53<sup>mut</sup>/KRAS<sup>mut</sup> patients (median OS of 10 and 15 years respectively) had significantly better OS than the co-occurring KRAS<sup>mut</sup>/TP53<sup>mut</sup> 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 demonstrate the existence of an extraordinary survivor cohort and 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 (HRadj) and 95% confidence intervals (CIs) are reported. **Results:** Pts who only received Oxa-based treatment reported the lowest rate of G3+ AEs (p < 0.0001) 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 < 0.001). 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-Iri (HRadj = 1.2, 95% CI, 1.1-1.3, p = 0.001) and tri-based regimens (HRadj = 1.4, 95% CI, 1.2-1.5, p = 0.001). 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 (HRadj = 0.86, 95% CI, 0.78-0.94, p = 0.016), whereas G3+ AEs were associated with a shorter OS (HRadj = 1.2, 95% CI, 1.1-1.4, p = 0.004) 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. We also explored the relationship between baseline circulating tumor DNA (ctDNA) and AEs with RAS mutations in 1,86s Gastrointestinal (Colorectal) Cancer
Conclusions: T variants (58), variants (in patients receiving cetuximab based chemotherapy, which may dependent genetic variations in sidedness related genes are associated with PFS and OS. Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

Background: Accumulating evidence suggests that right- and left-sided CRCs have different prognoses and different sensitivities to EGFR inhibitors in several phase 3 trials. These differences might be related to different embryological origins, which are reflected in different molecular profiles of tumors. LEFTY1, Nodal and ACRV2B, which are TGF-beta super family, 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 FOLIRI as first-line treatment and analyzed by using PCR-based direct sequencing. Four functional SNPs in 4 genes (LEFTY1, LEFTY2, Nodal, and ACRV2B) 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) 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% CI = 0.37-1.01, P = 0.048) and multivariate analysis (HR = 0.59, 95%CI = 0.35-0.99, P = 0.046). In patients with right sided tumors (N = 58), ACRV2B rs2268753 C/C vs. 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% CI = 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 depend on location.

Background: Patients with RC do not represent a uniform population. ETS represents a unique molecular subtype of patients. Further mechanistic research on clinical outcome. A supervised gene expression analysis revealed a prognostic subtypes.

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 demographic and tumor characteristics (stage, grade, margin, tumor location, node status, comorbidity score), and treatment (surgery, chemotherapy, radiotherapy, metastastectomy) 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.

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. 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 demographic and tumor characteristics (stage, grade, margin, tumor location, node status, comorbidity score), and treatment (surgery, chemotherapy, radiotherapy, metastastectomy) 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.

3585 Poster Session (Board #209), Sat, 8:00 AM-11:30 AM

Factors contributing to the black/white colorectal cancer survival disparity in nonelderly patients. First Author: Helminne 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 demographic and tumor characteristics (stage, grade, margin, tumor location, node status, comorbidity score), and treatment (surgery, chemotherapy, radiotherapy, metastastectomy) 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.

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. 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 demographic and tumor characteristics (stage, grade, margin, tumor location, node status, comorbidity score), and treatment (surgery, chemotherapy, radiotherapy, metastastectomy) 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.

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NRAS mts increased MAPK pathway activation above WT (range: 107%-211% of WT 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: 10.7%-211% of WT activity). Within the typical RAS mts, mts in KRAS or NRAS 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 V141, G22K, 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 in- crease activity (activity < 90% above WT). Pts with WT KRAS 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.

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 (spiculated flexure to rectum; n = 150) 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 test was used for comparisons. Results: LCCs from younger pts (median age 40, range 22-45 years) were younger (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), and 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 (18% of younger pts (7.7% v. 2.8%, P = 0.001)) and MDM2 amplification compared to younger pts (4.8% v. 0.5%, P = 0.015). MSH2(2.4% v. 0.0%, 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.

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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, Veje, 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 135 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 mutation in plasma. A substantial increase in ctDNA level was highly associated with progression on treatment (risk ratio = 4.55, 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: Mitsuku Suena, Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: EGFR signaling blockade increases CCL5 expression, which attracts 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 (CT)-based first-line treatment in metastatic colorectal cancer (mCRC) patients (pts). Genetic 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 FOLFOX4 (median age 64 yrs; median follow-up 34.1 mos); and a control cohort of 247 pts receiving FOLFOX4 (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 rs1799983 T allele had a trend lower response rate than those with the CC 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.

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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 assessing 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/KZF1 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 tumor clearance. Of the 35 postoperative ctDNA negative cases, 22 had further surveillance CT scans with no evidence of disease. Conclusions: ctDNA with a significant reduction in ctDNA after surgery suggests that ctDNA may be a useful biomarker to inform the completeness of resection given the high rate (74.5%) of ctDNA disappearance after surgery.

Results:

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Association of T-cell infiltration assessed in peritumoral 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, Brussels, Belgium

Background: Pre-operative CRT followed by total mesorectal excision (TME) is nowadays the standard of care for patient with LARC (ctT3-4N0 or cTcNx). 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 Saint-Luc. The density of CD3 (T cells) and CD8 (cytotoxic) was quantified 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 pathologic response (Dworak 3-4) and lower pT, pN and pM stages (p<0.05). Higher CD3 and CD8 PTB densities were associated with higher patient DFS (D3: HR = 2.30 (95%CI: 1.15-4.59), p=0.02; D8: HR = 1.95 (95%CI: 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: Peritumoral T-cell infiltration of LARC is predictive of tumor response and relapse after CRT + TME. This biomarker could be helpful in patient treatment decision. It must be validated in larger patient cohorts.
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 Doanhan, Laribosieire Hospital, Vascular 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 FOLFIRI 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 = 0.69 [95% CI: 0.60-0.77]), change rate in kurtosis (ssf = 0) (AUC = 0.66 [95% CI: 0.57-0.74]), and the baseline density of the DLL (AUC = 0.68 [95% CI: 0.59-0.77]). Using multivariate analysis, predictive factors of 2-year survival status were the decrease in STL > 15% (HR = 1.92, P < 0.002), the increase in kurtosis value (ssf = 0) > 95% (HR = 2.16, P = 0.001), and baseline DLL > 64.3HU (HR = 1.70, P = 0.02). Then, the SPECTRA-score was built by adding 1 point for each of the 3 criteria. Patients with a SPECTRA-score > 1 had a lower overall survival in the training (Pc = 0.001) and in the validation cohort (Pc = 0.02). 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 able to predict a non-response which patients have a poor outcome with same performances than standard evaluation with RECIST1.1 at 6 months in mCRC patients. Clinical trial information: NCT00952029.

FIFRI and bevacizumab using baseline and first evaluation CT and to compare it to the RECIST and morphological criteria. Results: Totally 406 patients were randomly assigned. Actually, 153 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 (150 [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, P < 0.001) and OS (1.0 [0.5-1.5] day, P < 0.001) days to first automatic urination (2.0 [2.0-3.0] day) than LAP (3.0 [2.0-4.0] day, P < 0.001). Also, RAP reduced incidence of incisional complications, with a reduced number of superficial (4.9% vs 8.4%, P = 0.032), deep (2.0% vs 4.9%, P = 0.033), and exit site infections (0.0% vs 1.6%, P = 0.046) compared to the LAP group. 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.

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 = 0.69 [95% CI: 0.60-0.77]), change rate in kurtosis (ssf = 0) (AUC = 0.66 [95% CI: 0.57-0.74]), and the baseline density of the DLL (AUC = 0.68 [95% CI: 0.59-0.77]). Using multivariate analysis, predictive factors of 2-year survival status were the decrease in STL > 15% (HR = 1.92, P < 0.002), the increase in kurtosis value (ssf = 0) > 95% (HR = 2.16, P = 0.001), and baseline DLL > 64.3HU (HR = 1.70, P = 0.02). Then, the SPECTRA-score was built by adding 1 point for each of the 3 criteria. Patients with a SPECTRA-score > 1 had a lower overall survival in the training (Pc = 0.001) and in the validation cohort (Pc = 0.02). 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 able to predict a non-response which patients have a poor outcome with same performances than standard evaluation with RECIST1.1 at 6 months in mCRC patients. Clinical trial information: NCT00952029.

Gastrointestinal (Colorectal) Cancer

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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 (FLCAP), 13183 (21.5%) in FOLFOX plus oxaliplatin (FOLFOX/CAPOX), 357 (0.6%) in uracil and tegafur/loxifluoridine (UFT/D) and 36443 (59.4%) in surgery alone. For patients with stage II and III CRC, the initiation of AC > 8 weeks after surgery was associated with a significant decrease in overall survival (OS) (FLCAP, 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 I CRC, receiving AC < 3 months regardless of chemotherapy regimens had a significant lower survival (FLCAP, 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 was associated with worse survival (HR = 1.13, 95% CI = 1.06-1.21). In a large national dataset, RSI was associated with worse survival (HR = 1.13, 95% CI = 1.06-1.21).

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 chemoradiation) 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-N0) of CRT followed by consolidation chemotherapy (capecitabine and oxaliplatin: CapOx) compared to that of CRT alone. Methods: Patients (pts) with adenocarcinoma of rectum ≤12 cm from anal verge), ECOG PS 0 or 1, and cT3-NxM0 were enrolled. CRT (50.4Gy/25-28x) with Cap (85mg/m²/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 after a week after completion of CRT before TME (Cap 850mg/m²/day from day 1 to day 14; Ox 100mg/m²/day 1; q3w). 110 pts (55 in arm A; 53 in arm B) were randomized and started study treatment. Median age was 56 years; male/ELOC PS 1ct4 was 76%/70%/18%. 100 pts (54 in arm A; 46 in arm B) completed CRT ≠ 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 outcome treatment is described in the 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.

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 chemoradiation achieves low local recurrence rates in locally advanced rectal cancer (LARC), it delays administration of systemic chemotherapy. About 30% of patients still develop distant metastases, which is the main obstacle for improving survival of LARC. Besides, preoperative radiography 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 chemoradiography.

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 was performed before and after 4 cycles of chemotherapy. 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 FOLOX was recommended. The primary endpoint is the ratio of tumor downstaging to ypT0-N0-NxMx. 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 chemoradiation, the pCR rate and tumor downstaging were 14.3% and 41.4%, respectively. And the chem-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 (LARC), it delays administration of systemic chemotherapy. About 30% of patients still develop distant metastases, which is the main obstacle for improved survival of LARC. Besides, preoperative radiography 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 chemoradiography.

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 was performed before and after 4 cycles of chemotherapy. 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 FOLOX was recommended. The primary endpoint is the ratio of tumor downstaging to ypT0-N0-NxMx. 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 chemoradiation, the pCR rate and tumor downstaging were 14.3% and 41.4%, respectively. And the chem-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.

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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 abstr#3617). Methods: A total of 991 patients with curatively resected stage II colon cancer (2006-2010; 196 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 mm²) 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 nodes 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.

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 abstr#3617). We herein examined 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 univariate and multivariate proportional hazard model. Among 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.

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Microbiota as a new indicator of colorectal cancer (CRC) heterogeneity. First Author: Iraj Sabhani, Department of Gastroenterology and Oncology, Hospital 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 CRC families. "MICAT" pipeline was used, library sorted (Phred quality score >20 Ailentrimmer 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. Differences between Control (N = 87) and CRCs (N = 69), between L (N = 19) and S CRCs (N = 50), and between LCR-CRC (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 kapa) 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 in MSI, C-CRC and L-CRC, C-CRC and first degree relatives based on the common component (similarity of sequences): 13 species differentiated Normal and CCs, two were more prevalent in L-CRCs. The panels of bacteria linked with location, MSI, Ras mutations, methylation phenotypes and survival were identified.

Conclusion: CRC dysbiosis is location-dependent. Several bacteria are associated with MSI and methylation status. They may directly or through therapies impact the prognosis. Microbiota signature should be taken in consideration in trials.
Gastrointestinal (Colorectal) Cancer

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 ≥ 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 Q6W 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 nab-paclitaxel (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. Nab-paclitaxel is a first-in-class cancer stemness inhibitor in development identified by its ability to inhibit STAT3-driven gene transcription and sphegerogenesis of cancer stem cells (Li et al, PNAS 112(6):1839, 2015). Preclinically, nab-paclitaxel sensitizes cancer cells to chemotherapeutics, including 5-FU and irinotecan. Encouraging antitumor 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-naive pts who had 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 nab-paclitaxel+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 nab-paclitaxel 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 is met. Key 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 DOR 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.

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**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 phase III study of BEACON plus CTX plus or minus BINI vs irinotecan (IRI)/CTX or infusional 5-Fu/Leucovorin/Infusional Irinotecan (FOLFIrIX) without a safety lead-in of BINI + CTX in patients (Pts) with BRAF**

**Background:** BRAF mutations are found in ~10% of mCRC cases. Pts with BRAF**

**Methods:** BEACON CRC (NCT02928224) is enrolling pts with BRAF**

**Conclusion:** Our study will examine the combination of BINI (a MEK inibitor) + ENCO (a selective BRAF kinase inhibitor) + CTX (an anti-EGFR antibody) and of ENCO + CTX in pts with BRAF**

**TPS3623**

**Poster Session (Board #243b), Sat, 8:00 AM-11:30 AM**

**Multicenter phase II trial of BB1608 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/b-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/b-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 BB1608, which blocks STAT3 and WNT/b-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 BB1608 (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 (iORR) 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 tissue and blood 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.

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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 or 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 I, 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 use to avoid overlapping toxicity, notably decreased neutrophils due to oxaliplatin or trifluridine/tipiracil. Trifluridine/tipiracil is administered orally (cohort 1: 25 mg/m² bid; cohort 2: 30 mg/m² bid; cohort 3: 35 mg/m² bid) from day 1 to 5; and oxaliplatin at 85 mg/m² (with a possibility to reduce to 65 mg/m²) 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/m² bid and oxaliplatin 85 mg/m²). 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.

Gastrointestinal (Colorectal) Cancer

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 (IIA vs IIB vs III), any prior pelvic surgery or perineal perineum (yes vs no) and independent activity of daily living score (IADL: normal vs abnormal). Arm A and D receive LV5FU2 or capecitabine, arm B FOLFIRI 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 resection and then annually for 2 years. Hypotheses for co-primary outcomes: DFS (90% power) vs control (80%). Methods of analysis: 3-years DFS from (arm A) to 72% vs 55% (arm D) in group 2 (756 patients required) and from 40% (arm C) to 55% (arm D) in group 2 (222 patients required). Safety is evaluated based on laboratory and clinical tests before each cycle. Exploratory analysis are planned to determine genetic prognostic factors for DFS. A biological ancillary study is planned to allow prognosis evaluation of mismatch repair status and other molecular signatures. At the 1st of February 2017 the accrual was 246 patients. Clinical trial information: NCT02355379.

TPS3627 Poster Session (Board #24b), 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: Deidre 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/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 ≤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 (overall response rate and progression-free survival), and obtaining pharmacokinetic parameters. Pre- and on-treatment biopsies will be collected from the expansion cohort to determine: adequate 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: NCT02906195.
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. Sniecure, Mayo Clinic Cancer Center, Rochester, MN

**Background:** In metastatic colorectal cancer with deficient DNA mismatch repair (dMMR), 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 Mesorectal 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 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 (lTaTME) for low rectal cancer. Patients diagnosed with clinical stage no more than T3NO or T3N2 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 lTaTME. 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 to CRT. 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/m2 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 beta = 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
EORTC15271/IC0G16091NT: Diffusion-weighted MRI (DW-MRI) assessment of liver metastases 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, ESIO and JCOA 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<0.85 and is powered under the alternative that the NPV>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.

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Clinical trial information: NCT01755767. 120mg BID dose did not improve OS or PFS over placebo in patients with G3.

Conclusion: 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 (NCT01757567) 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), extraparenchymal 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%) median age: 67; PS: 0/1 (67); VI; 117 (34%); ES: 179 (58%); AFP ≥200: 195 (57%); radiographic PD on sorafenib: 275 (81%); Median OS (95% CI) was 8.6 months (6.0-10.0) in T, 9.1 months (7.6-10.6) in P (HR 0.92, 95% CI 0.75-1.12), P = 0.25. Median PFS (95% CI) was 2.1 (1.9-3.0) in T, 2.0 (1.9-3.0) 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 0.91, 0.78-1.05), AFP > 200ng/ml (HR 1.00, 0.71-1.41). Grade (G) ≥ 3 AEs were 56.6% 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% in T vs 15.8% in P (most common causes: general deterioration 34.3%, hepatic failure 26.6%). 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.

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 SIReNIB 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 (EHM). Methods: This investigator initiated trial randomized eligible patients with locally advanced inoperable HCC to single injection of Y90 or sorafenib (oral 400mg BID) 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 360 patients (182 Y90, 178 sorafenib) were randomized 1:1 to LEN (body weight ≤60 kg: 12 mg/day; > 60 kg: 15 mg/day) or SOR; as first line therapy for uHCC, TEAEs were consistent with the known LEN safety profile. Clinical trial information: NCT01761266.

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: Pembrolizumab has shown promising antitumor activity and manageable safety in a phase 1 study of pts with previously treated advanced gastric cancer [1]. 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 with measurable recurrent or metastatic G/GEJ adenocarcinoma who had progressed on ≥2 prior lines of therapy. Pts were randomized 1:1 to pembro 200 mg Q3W up to 2 y or up to disease progression. Safety endpoints were assessed in the ITT population. 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, 12.6-22.0) 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+). 14.9% (95% CI, 9.4-22.1) in 3L pts and 7.2% (95% CI, 3.3-13.2) in 4L+. In 3L 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, 8.0-19.1) PR; in PD-L1+ pts was 5.5% (95% CI, 1.6-14.1) (liver-specific) (HR 0.77) (95% CI, 0.1-4.6) (liver-specific) (HR 0.77). Grade 3-5 toxicities were 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, 1.9-26.7), 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 (abdominal LFT, bile duct stenosis) and were fatal in 2 pts (acute kidney injury, pleural effusion). Conclusions: Pembrolizumab showed encouraging efficacy and was tolerable as 2nd or 3rd line of therapy for patients with G/GEJ cancer in this large phase 2 trial. Survival and additional biomarker data, including MSI status, will be presented. Clinical trial information: NCT02335411.
Gastrointestinal (Noncolorectal) Cancer

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/EXC) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-A01): A multicenter, randomized, investigator-initiated, phase 3 trial. First Author: Sahlah-Eden Al-Batran, Institute of Clinical Cancer Research (IKF) at Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany
Background: The MAGIC trial established perioperative (perip) epirubicin, cisplatin, and 5-FU (ECF) as a standard treatment for patients (pts) with operable esophagogastric cancer, but survival continues to remain poor. FLOT (NCT01216644) is a multicenter, randomized, investigator-initiated, phase 3 trial. It compares the docetaxel-based triplet FLOT with the anthracycline-based triplet ECF/EXC as a perip treatment for pts with resectable gastric or GEJ adenocarcinoma. Methods: Eligible pts of stage I-IVC and/or CN+ were randomized to either 3 preoperative and 3 postoperative 3-week cycles of ECF/EXC (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 preoperative and 4 postoperative 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/EXC; 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/EXC and 90% and 50% with FLOT completed planned preoperative and postoperative cycles, respectively. Median follow-up was 74% (95%CI 69, 77%) and 82% (95%CI 77, 87%) of pts with ECF/EXC and 100% and 90% with FLOT. There was more G3/4 nausea and vomiting with ECF/EXC (38% vs 18% in FLOT). Conclusion: FLOT improved OS (mOS, 29.9 vs 26.9 months (mos). OS was estimated by the Kaplan-Meier method & arms compared using the log rank test. Cox proportional hazards model was used to analyze treatment effect. Results: 336 pts were randomized from 11/7/2009 to 2/28/2014, with 163 pts evaluable for G and 159 for G+. Median age was 59 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+G arm, respectively. There are fewer grade 3 GI AEs (39% vs 51%), grade 3 G+ arm (28%), and (69.2%) & 93 (59.6%) pts received at least 85% of planned G dose for the G & G+E arms, respectively. 58% of G+ pts received at least 85% of planned G dose. The median follow-up for alive pts is 42.5 mos (min-max: 1.04). Conclusion: The addition of adjuvant E to G did not provide a survival benefit 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.

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/m² 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 α = 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 patients 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 ECOSG 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%). Follow-up was 369 months (mos). FLOT and Cape was 369 mos (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, CR) 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: isrCTN7785446.

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A randomized phase II pilot study prospectively evaluating treatment for patients based on ERCC1 for advanced/metastatic esophageal, gastric, or gastroesophageal junction cancer (ESGC). R梳理性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 un-treated 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, and when compared with IT, in pts with ERCC1 <1.39, FOLFOX, PFS and RR was superior statistically to IT. No tumor cell difference in OS. There was no significant evidence of differential treatment effect on PFS across ERCC1 levels. Clinical trial information: NCT01498289.

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/FU (CF) +/- panitumumab (P) for patients (pts) with non-resectable, advanced, or metastatic esophageal squamous cell cancer (ESCC): An open-label, randomized AIO/TTO/BDG0/EORTC phase III trial (PIPER). 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 with limited impact. Prior studies suggested improved median OS in pts treated with a cisplatin-fused efficacy of EGFR antibodies (AB) combined with CF (Lorenzen, Ann Oncol 2009). Methods: This open-label, randomized (1:1), multicenter, multi-phase III included pts with non-resectable, advanced or metastatic ESCC (RECIST 1.1), not radiochemotherapy (RCT) eligible and ECOG PS 0-1. Previous CTX in metastatic setting, concurrent RCTX and exposure to EGFR-inhibitors were exclusion criteria. OS, PFS, ORR (RECIST 1.1, by central review), DOR, PFS, and OS (secondary). Results: Between 6.2012-5.2015, 146/155 pts were randomized. After interim analysis for futility, the trial was stopped. 60% treated CF and 40% treated CF/P. Grade 3/4 skin reactions and rash were higher in CF/P (10%) vs CF (0%). Overall, 51/72 (71%) of CFP and 36/70 (51%) of CF had SAE. Main SAE were dysphagia, fatigue 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, and when compared with IT, in pts with ERCC1 <1.39, FOLFOX, PFS and RR was superior statistically to IT. No tumor cell difference in OS. There was no significant evidence of differential treatment effect on PFS across ERCC1 levels. Clinical trial information: NCT01498289.

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-Chieh 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), and updated safety data from KEYNOTE-059 cohort 2. Methods: 200 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) on pembro 200 mg on day 1 of a 21-day cycle, and q1w nab-PTX (100 mg/m²) or q1w sb-PTX (80 mg/m²) on days 1, 8, and 15 of a 28-day cycle. The primary objective was to evaluate whether q3w nab-PTX and q1w sb-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 defined as the time between each 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 10.5, 11.1, and 10.9, respectively. Q1w nab-PTX was non-inferior to q1w sb-PTX (hazard ratio 0.97, 95% CI 0.73-1.31; non-inferiority one-sided p = 0.0089), 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 comparison, q3w nab-PTX showed favorable effect in comparison with q1w sb-PTX in terms of response rate of target lesions at best response and time to 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 AGC with AGC. Clinical trial information: 132059.
Nivolumab (nivo) in sorafenib (sor)-naive and -experienced pts with advanced hepatocellular carcinoma (HCC): CheckMate 040 study. First Author: Todd P. obligons, 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 (ESC) phase of the CheckMate 040 study (NCT03167165, 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, 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 (B18) 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) was 16%–19%. Key eligibility for CC: recurrence of progressive disease ≥6 mo after prior SOC therapy (dose escalation) or at least a prior clinical trial in mIDH1 solid tumors, in- cluding CC of mIDH1 CC following standard therapy or at least a prior gynecologic-based regimen (expansion cohort). Response (RECIST 1.1) was assessed every 8 weeks. Plasma and tumor tissue were collected for ex- ploatory analyses. Results: Based on the safety, pharmacokinetic, and pharmacodynamic data from dose escalation, the 500 mg QD dose was selected for expansion in CC and pts with mIDH1 solid tumors. As of Dec 16, 2017, 73 pts with mIDH1 CC had been dosed in the dose escalation (n = 24) and expansion (n = 49) cohorts. Demographics: M/F = 44/29, median age 62 y. Treatment-related toxicities. Repeated-measures analysis in ≥5%; 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 dose-limiting toxicities. Treatment-related adverse events ≥AEs of grade ≥3 were: rash (3%) and fatigue (2%). No treatment-related deaths occurred. 4 pts (8%) experienced treatment-related adverse events ≥3 in ≥5% of pts: fatigue (21%), nausea (18%), vomiting (12%), diarrhea (10%), decreased appetite (8%), dysgeusia (5%), QT prolongation (5%). Two (3%) pts experienced grade ≥3 AEs: fatigue and low phosphorus.

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 GEJ cancer (NCT01658878; 5.3 vs 4.1 mo; HR: 0.63; P < 0.001; ASCO-GI 2017, Kang YK et al. J Clin Oncol. 2017;35(suppl 45) (abstract 2)). Here we present updated long-term follow-up data of GEJ pts in CheckMate 032. Methods: Pts received N 3 mg/kg Q2W (N3), N1 mg/kg + 13 mg/kg Q2W (N1+13), or N3 mg/kg + 11 mg/kg Q2W (N3+11). Primary endpoint was ORR. Secondary endpoints included DOR, DCR, OS, and safety. Efficacy in pts by PD-L1 status was assessed. Results: 160 heavily pre- treated pts (79% had ≥ 2 prior Tx) were enrolled (N3, n = 59; N1+13, n = 49; N3+11, n = 52); 24% had PD-L1 (≥ 1%) tumors. ORR was 12% in N3, 24% in N1+13, and 13% in N3+11. In pts with PD-L1 ≥ 1%, ORR was 19% (3/16) in N3, 40% (4/10) in N1+13, and 23% (3/13) in N3+11; 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+13, and NA in N3+11. 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+13, 14%; N3+11, 2%), ALT increased (N3, 3%; N1+13, 14%; N3+11, 4%), and AST increased (N3, 5%; N1+13, 10%; N3+11, 2%). Conclusions: N = 1: led to durable responses and long- term OS in heavily pretreated Western pts with adv GEJ/E 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 in pts with adv GEJ/E cancer. Clinical trial information: NCT01289394.

OS in all pts and pts with PD-L1 ≥ 1%.

<table>
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<th>OS 2Y</th>
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<td>7.9</td>
<td>13 (13)</td>
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</tr>
<tr>
<td>PD-L1 &lt; 1%</td>
<td>9 (9)</td>
<td>7.1</td>
<td>11 (11)</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>

Conclusions: DORs were durable and OS benefit was seen regardless of PD-L1 status. OS benefit was maintained beyond 2 years in N3 and N1+13, and similar to placebo in N3+11. Nivolumab monotherapy improved OS and durable responses in GEJ cancer pts, which is consistent with that observed in Asian pts. Updated OS data are available at visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Phase III study of individualized intraoperative/intraovarian 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. Intraoperative (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(V)/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 (BRCAl/TOPOI/TS) to choose sensitive chemotherapeutics from oxaplatin/cisplatin/docetaxel/netotecav-L-1 and then received individualized IP/V/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 well 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.

Gastrointestinal (Noncolorectal) Cancer

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 microsatellite loci 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 0-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 did not improve 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 = 0.89). In conclusion, the 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.

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 Agilent Diagnostics Xcel array and the expression levels of PD-L1 probesets corresponding to protein encoding transcripts were measured. Results: High PD-L1 expression in the pre-therapy biopsies was associated with pathological response (TNG ≥ 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 (p = 0.001) correlated with tumor 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 expression was associated with the best 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 expression levels of PD-L1 probesets corresponding to protein encoding transcripts. Response was measured using the Almac Diagnostics Xcel array and the expression levels of PD-L1 were measured using the Agilent Diagnostics Xcel array. Results: Between April 2013 and December 2015, 231 patients were enrolled, and 218 patients were included in the efficacy analysis. Baseline patient characteristics were well 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.

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(+). First Author: Jeeun 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.
Background: Immuno-oncology (IO) with anti-PD-1 and -PD-L1 antibodies (Abs) is active in EGCG 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/L-PD-L1 Abs and correlated their outcomes with PD-L1 and mismatch repair defect (MMR) status by immunohistochemistry (IHC), as well as MSK-IMPACT (340-gene) NGS profile. MSI/Germ by IMPACT assesses microsatellite instability phenotype, whereas ≥20 mutations/Mb strongly correlates with MMR-deficiency (dMMR) by IHC. U Clin Oncol 2016;3:42-141. 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 adenosCA and 5 had squamous CA. Median age 58, 77% male, 96% had received ≥2 prior chemos 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/L-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%; ≥1% of tumor cells). 6 Pts (8%) had objective response (≥30% decrease of target lesion on Images) and 2 of 6 had ≥1% PD-L1 expression. Conclusions: PD-L1 expression is predictive of IO response and can be applied to routine diagnostic material.

Gastrointestinal (Noncolorectal) Cancer

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 esophagealgastric cancer (EGCG) patients. First Author: Geoffrey Yuat Ku, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Patients with esophagealgastric adenocarcinoma (EAC/GAC) treated with anti-PD/L1 are heterogeneous. Some patients 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. Turckington, 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 complete response rate (p = 0.004) and a higher rate of tumor regression (CR; p = 0.017) and the rate of distant relapse (30% vs. 20%; p = 0.013). For 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 endoscopy in EAC and can be used to help guide therapy in GAC and can be applied to routine diagnostic material.
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 (LJSSG0901). 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). Similar patterns were observed for 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 should be accepted with increasing morbidity complications in this setting. Clinical trial information: UMIN00003420.

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 survival 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 (LV+), 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. LV+ 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 observed for risk of death. 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 LV+ govern early survival events but as time from surgery increases these factors become less relevant.

Probability of relapse within timeframe conditional on RF status.

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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 and PD1 expression, and outcome in patients with esophageal 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 resection specimens were collected from each patient. Hematoxylin eosin (H&E) stain from each specimen was reviewed. PD1 was scored as either low or high expression whereas PDL1 expression was categorized as trace-low (TL) or moderate-high (MH) expressors of PDL1. We analyzed the expression of PDL1 and PD1 by immunohistochemistry for the expression of PD1 and PDL1. 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 PD1/PDL1 in matched samples was determined by regression analysis. Results: Following CRT, PD1 and PDL1 expression increased in 54% and 32% of patients, respectively. On multivariable 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 1.0-10.35; p = 0.039). In patients with TL expression before CRT, 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 PD1 and PDL1. 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 National Cancer Database (2004-2013), 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/adjunct therapy (n = 291, 2.6%) were compared for all four groups. On multivariable analysis, treatment modality had the largest impact on OS following 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/adjunct 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 esophageal confined tumors 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 adjunct 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.
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 ± 2.27 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 vs. 4.94 ± 4.87 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 = 0.011). 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 controls 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.

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 with endoscopic resection (Eso), and endoscopic resection (Eso). Multivariate Cox proportional hazards modeling were reported. Results: A total of 4,254 patients were observed, 14% underwent CRT, 23% LE, and 42% Eso. Median age and follow up were 67 days 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, income level, type of facility (academic vs. non-academic), and distance from receiving 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 < 0.001), which increased to 1.4% and 5.5% at 90 days (P < 0.001). Five-year OS was 21% for Obs, 26% CRT, 64% LE, and 63% Eso (P < 0.001). Multivariate analyses demonstrated improved OS for all of these, 2% of local definitive therapy: CRT (HR: 0.54, 95% CI (0.48-0.61), P < 0.001), LE (HR: 0.24, (0.20-0.27), P < 0.001), Eso (HR: 0.31, (0.28-0.35), P < 0.001). 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.

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Exclusive chemoradiotherapy with or without dose escalation in locally advanced esophageal carcinoma: The CONCORDE study (PRODIGE 26).

**Background:** In esophageal cancer (EC), 20 to 45% of patients suffer from local failure after 50 Gy 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 40 Gy elective nodal irradiation with either a 10 Gy boost (Arm A) or 26 Gy 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:** Endpoint. All analyses were performed in intent-to-treat. Quality of life according to the EORTC QLQ-C30 and OG25 was a secondary phase II was acute toxicity according to the NCIC-CTCAE (version 4.0). Patients were randomly assigned between Jan 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 86.6%, 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 69.9 (sd = 23.1) in arm A (p = 0.10) and 65.2 (sd = 19.5) vs 58.8 (sd = 19.9) in arm B (p = 0.16). The presence of dysphagia was neither significantly different between arm A (89.2%) and arm B (86.1%) (p = 0.61) at baseline nor at 3 months (77.8% vs 86.4%, p = 0.29). Odynophagia was present at baseline in 78.4% in arm A and 75.8% in arm B (p = 0.73) while the rates observed at 3 months were 68.1% 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.
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 18F-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 N1MO 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; IV, 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 of 635 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.
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: Multivariable 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/EJ) 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/EJ 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] ≥ 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/EJ 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 naive G/EJ 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 naive and previously treatedadvanced G/EJ 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 QLQ instrument for cancer patients (pts), but there is limited information for gastric cancer. To identify priority domains and determine 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 QLQ domains were compared by best overall response (BOR) and ECOC performance status (PS) using analysis of covariance. Odds ratios (ORs) for BOR and PS outcome group per QLQ unit (point) change were estimated by cumulative log re- gression modeling, with ORs<0.80 considered meaningful. Results: Changes from baseline in QLQ 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.

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 pali- liative chemotherapy and targeted therapy for metastatic EGC. Prognostic and predictive factors were identified from respectively multivariate cox regression models, with OR<0.80 considered meaningful. Results: Changes from baseline in QLQ domains were significantly associated with BOR and PS outcomes. 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.

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 regression models, with OR<0.80 considered meaningful. Results: Changes from baseline in QLQ domains were significantly associated with BOR and PS outcomes. 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.

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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 Jumaan 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 have a high risk for radiation-induced cardiotoxicity. Methods: Esophageal cancer survivors (defined as surviving > 5 years 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]: 7.1-12) 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 yrs (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: 1.5-2.6; 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.

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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 (66%) 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 0.21, 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.

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%) were adenocarcinoma (AC). All patients were treated with intense radiation 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 74.4% 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; R² = 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.

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 sample means were compared to 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 33.6% 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, 63.9% 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 C, 5.2% married AAs, 6.6% single Cs, and 6.5% single AAs) along with surgery refusal rates (1.5% 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.
Gastrointestinal (Noncolorectal) Cancer

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 a induction cycle of cisplatin 100 mg/m², day 1, and 5-FU 1000 mg/m²/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/m² and escalating doses of CI 5-FU, days 1–4 and 29–32. Pts received also 10 weekly infusions of cetuximab, 250 mg/m², with a loading dose of 400 mg/m², 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, RO resection was achieved in 51 (93%). There were 8 cases (14.5%) of postoperative mortality, due to infection (3 pts), sepsis (2), postoperative bleeding (2) and pulmonary insufficiency (1). Pathological down-staging was noted in 72% of pts and pathological complete response (pCR) in 33%. 5-y local control, progression-free survival (PFS) and overall survival (OS) for all pts were 94%, 40%, 39%, respectively. Pts with SqCC had a significantly higher pCR rate (52% vs 15%, p = 0.007), 5-y PFS (67% vs. 21%, p = 0.008) and OS (64% vs. 20%, p = 0.019). Conclusions: This study suggests that the addition of cetuximab to standard preoperative CRT is safe. RO, 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 excised 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 ratio for death in patients with 16–29, 30–44 and ≥45 examined lymph nodes were 0.97 (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 suggest that 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 resections performed for gastric cancer. This finding is concerning due to the majority of patients do not respond. Therefore, a rationale strategy of combining immunotherapeutic agents with CRT in early 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 and flow cytometry to assess the changes in tumor infiltration of immune cells. Results: Conclusions: Overall, the majority of the patients who underwent neoadjuvant CRT showed an increase of CD8+ T lymphocytes at the tumor stroma interface. These tumors also demonstrated high expression of galectin-3, a marker of the epithelial–mesenchymal transition, and E-cadherin. These findings provide insights into the evolving immune landscape after CRT and may have implications for future neoadjuvant trial designs that could enhance radiotherapy with immune checkpoint inhibitors. Collectively, these findings provide insights into the evolving immune landscape after CRT and may have implications for future neoadjuvant trial designs that could enhance radiotherapy with immune checkpoint inhibitors. Currently, we are conducting a neoadjuvant trial assessing Nivolubum or Nivolubum/piolumab in combination with CRT in stage III/IV operable esophageal cancer.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 surgery. Sequential perioperative chemotherapy was utilized in 20%, surgery alone with approximately 53% of these patients diagnosed with stage I gastric cancer. The secondary endpoint included objective response rate and 1-year OS. Ruinuo Jia and Tanyou Shan did equal work. Clinical trial information: NCT01784900.

### Table 1: Breakdown of treatment for gastric cancer.

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th># of Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery alone</td>
<td>7,685</td>
<td>44.6</td>
</tr>
<tr>
<td>Postop Chemotherapy alone</td>
<td>294</td>
<td>1.7</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>1,183</td>
<td>6.6</td>
</tr>
<tr>
<td>Sequential periop</td>
<td>112</td>
<td>0.6</td>
</tr>
<tr>
<td>Concurrent</td>
<td>592</td>
<td>3.4</td>
</tr>
<tr>
<td>Neoadjuvant and adjuvant</td>
<td>982</td>
<td>5.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>264</td>
<td>1.2</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>26</td>
<td>0.1</td>
</tr>
<tr>
<td>Total</td>
<td>17,656</td>
<td>100</td>
</tr>
</tbody>
</table>

4061 Poster Session (Board #53), Sat, 8:00 AM-11:30 AM

A randomized, open-label, multicenter trial of the concurrent chemoradiotherapy of capecitabine with or without oxaliplatin via 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 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/20fr for all. Pts were stratified by different regimens. Both grade-3 ATs and 2-year OS were the primary endpoint, with a planned accrual of 249 pts to detect a decrease in Grade-3 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 2013 to 2014. 71 pts (55%) experienced 289 ATs (113 grade 3 and 4). The first end-point was the 2-year OS. Forty randomized patients were required (20 in each arm), considering that a 2-year OS rate ≤ 30% would be considered as unacceptable, and ≥ 55%, a promising survival rate. The study was stopped prematurely due to the manufacturing stop of the capecitabine. Conclusions: This nationwide screening system is efficient to detect rare gene alterations in EC. A novel knowledge providing an intriguing background to generate new target approaches and represents a progress toward more precise medicine. Clinical trial information: UMIN000018344.

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 receive chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCR) 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 Oncome 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 OCR 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 58.0%, squamous cell carcinoma 92.4%. The frequently detected mutations in 114 samples of which results were available were TP53 (77.2%), NFE2L2 (23.3%), CDKN2A (6.9%), PIK3CA (7.0%), RB1 (6.1%), and CNVs were CCND1 (37.7%), EGFR (7.9%), MYC (7.9%), MOKX1 (5.3%), MOKX1 (5.3%), ERBB2 amplification was identified in 3 cases (2.6%) and FGFR3-TACC3fusion was identified in one case (0.9%). Conclusions: This nationwide screening system is efficient to detect rare gene alterations in aEC. A novel knowledge providing an intriguing background to generate new target approaches and represents a progress toward more precise medicine. Clinical trial information: UMIN000016344.
Incidence rate and clinical-pathological features of hereditary diffuse gastric cancer patients in China. First Author: Miaoqun Qiu, Cancer Center of Sun Yat-Sen University, Guangzhou, China

Methods: Approximately 1-3% of gastric cancer arises in the setting of hereditary cancer patients in China. Incidence rate and clinical-pathological 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 7th TNM 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 +++. 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.

Gastrointestinal (Noncolorectal) Cancer

Background: FGRF2b-overexpressing gastric cancer is characterized by poor prognosis. FPA144, a humanized monoclonal IgG1 antibody that specifically binds to and blocks FGRF2b, 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 1A to assess PK in gastric cancer. Part 2 includes 4 cohorts of gastric cancer patients with either high, moderate, low or no FGRF2b overexpression based on a centralized immunohistochemistry (IHC) assay. Here, we describe results of gastric cancer patients that highly overexpress FGRF2b (FGRF2b+ High) enrolled in Parts 1 and 2 of the study. Results: As of October 28, 2016, 18 FGRF2b+ 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 (CR+PR+SD) was 51%, and lower incidence of grade 3/4 anemia (2.7%) and 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 31(1.4%) patients in TF group died of acute pneumonitis. For long-term AE, 10(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.
**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 fluorouracil 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 end-point of the study. Median PFS and OS was 2.0 months (95% CI, 1.6 to 3.2 months) and 9.0 months (95% CI, 6.4 to 11.7 months), respectively. 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 alteration status will be presented. Clinical trial information: UMIN000011217.

**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-PO-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, 3Q4 for 12 months or until confirmed progressive disease, rash, 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:** At data cut-off, 40 HCC pts with HCC, particularly HCV+ pts. Clinical trial information: NCT01693562.

**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 (capetibine 1g/m² twice daily/1-14 days and docetaxel 75mg/m² in 1st day) or XELOX (capetibine 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 neutropenia (1.5% v 1.5%), anemia (10.1% v 10.6%), 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 neurotoxicity, 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 platinum. Clinical trial information: NCT01963702.

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Gastrointestinal (Noncolorectal) Cancer

4073 Poster Session (Board #65), Sat, 8:00 AM-11:30 AM
Phase 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 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 mg 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 ≥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 ALT and ALT), 16 due to progressive disease, 4 due to death unrelated to study treatment, 1 due to valvar heart disease, 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 subgroups. Enrollment to the phase II portion of the study is ongoing. Clinical trial information: NCT02519348.

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 (JU-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 I study in advanced solid tumors (NCT01703481). Here we report results from pts with CCA from this study. Methods: This 4-part study enrolled pts aged ≥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 28-day AUC, in CCA pts was similar to other indications. The most common AEs were somatostatin (82%), hyperphosphatemia (64%), dry mouth (55%), dysgeusia (45%), dry skin (45%), and anemia (45%), mostly grade 1/2 severity. No dose-limiting AEs or other FGFR-related AEs were reported in ≥3 AEs in this group. Part 2 extension treatment (cardiac toxicity, valvar heart disease, progressive disease, probable HCC rupture) and 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 subgroups. Enrollment to the phase II portion of the study is ongoing. 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, the study was designed for 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; 40 were enrolled; 40 were enrolled; 40 were enrolled; 150 mg and 230 mg were enrolled at 300 mg dose level. Median age: 65%; Female: 74%; White: 85%; Gallbladder cancer 37%; intrahepatic cholangiocarcinoma 59%; 3 pts had prior G; 2 pts with advanced G; 1 pt with 2 prior regimens. Median number of cycles with D: 8 (range 1, 17). Median duration on study 6.8 mos; 6 pts still on therapy. No dose limiting toxicities or D-related serious adverse events have been observed. 24 (80%) of 9 pts 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), 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 advanced BTC. D + GC was 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 45 gene, mean coverage and 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, adenocarcinomas, or carcinomas not specified (NOS), respectively. Commonly altered genes were TP53 (62%), CDKN2A (31%), ARID1A (18%), and SMAD4 (15%), and most of the genetic aberrations (GA) were short variants. Potentially targetable SCNAS (including ERBB genes, MET, FGFRs, and the CCND1-FGF3/4/19 11q13 amplicon) were identified in 21% of cases (Table). Oncogenic BRCA1, 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. Radiologic 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/INI1mutations 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.

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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 (MI) 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 MI 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 MI using clinical data and preoperative setting.

Methods: HCC patients who consecutively performed HR or LT from January 2000 to 2016 were included. The outcomes of the HR and LT patients with high or low MVI probability were compared using log-rank test. The data are presented as median and interquartile range.

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 (>3.2 (p = 0.002), aspartate aminotransferase >62U/l (p = 0.02) were independently associated with MI. Of these factors, aspartate aminotransferase and largest tumor size were selected for the development of a predictive model using a Cox proportional hazards model. The predictive effect was modeled as a step function.

Conclusions: This model developed from preoperative data allows reliable prediction of MI, and may thus help with preoperative decisions about the suitability of HR or LT in patients with HCC.

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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 0-1 and 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 of ≥3.5 months as evidence of the study drug activity (α = 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 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. Median PFS of 30 patients who had 3 or more cycles was 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 1 (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 selection of 500 mg QD for future clinical investigation. Clinical trial information: NCT02053376.

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 A. 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 400 mg/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 S. Mean dose of S was MD Anderson Cancer Center (MDACC) doses < 50%, 50-75% & > 75%. 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%). 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). Survival outcomes were assessed with univariate & 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 50-75% S appears to have a superior median survival, though this is not significant after controlling for baseline characteristics.
A prospective analysis of germline alterations (GA) in biliary tract cancer (BTC). First Author: Mavee Aine Lowery, 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 analyzed 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 pts 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.

<table>
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Conclusions:
A pre-PRRT analysis of circulating NET genes, the predictive marker by multivariate analysis (p < 0.002). The PQI diagnostic was 2.2 GBq). NETs (n = 35); with progressive disease (66%)

Background:
The incidence and prevalence of neuroendocrine tumors (NETs) (defined as either small volume progression (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-NET control cohort. With these algorithms, we set two cut-off values (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-NET control cohort. With these algorithms, we set two cut-off values
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 68Ga-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: PRRT represents a step change in NET management, signifying significantly improved survival. However, objective response to PRRT is approximately 20%, is poor. There are no predictive biomarkers of response. Uptake on 68Ga-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: We hypothesise that the density of SSTRs, as defined by a minimum SUV uptake, predicts for response to PRRT. We performed a phase I study to evaluate the safety and radiation dosimetry of the sstr2 antagonists 68Ga-DOTATATE and 177Lu-OPS201 (68Ga-DOTATATE and 177Lu-OPS201). This study was conducted in a phase I/II clinical trial of 68Ga-DOTATATE and 177Lu-OPS201. In patients with metastatic well differentiated NETs, 68Ga-DOTATATE was used to calculate tumor and normal organ radiation doses. Dosimetry was then calculated to administer 177Lu-OPS201 divided doses for the 2nd and 3rd fractions, 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 177Lu-OPS201, 7 pts received 2 doses. All tumors were visualized by 68Ga-DOTATATE PET/CT. With the exception of the kidneys and bladder, no organ demonstrated uptake of 68Ga-DOTATATE above background. Tumor radiation doses ranged from 0.15 Gy/Ci to 0.48 Gy/Ci. Subacute hematologic toxicity after cycle 1 was mild-moderate (G3/29 leucopenia that reversed before cycle 2). G4 (57%) pts that received the second dose of 177Lu-OPS201 had G4 hematologic toxicities, which occurred 4-6 weeks after administration. G3/4 toxicities in the remaining 4 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% PD (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 68Ga-DOTATATE and 177Lu-OPS201 as a therapeutic combination for imaging and therapy. Additional studies are planned to determine an optimal therapeutic dose and schedule. Clinical trial information: NCT02690737.

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: Alexandros T. Phan, University of New Mexico Comprehensive Cancer Center, ~0.15, 99, NCI 0.71-3.96. No association between baseline SUVave and SSTR2 or Ki-67 was observed. SUVave.

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 in those with PD. Response (PR) 26%, stable disease (SD) 40% progressive disease (PD) 12%.

Conclusions: Objective response to PRRT defines a subset of patients with marked improvement in PFS. Uptake in clinical practice. We observed a positive association between baseline SUVave and SSTR2 or Ki-67.

Background: PRRT represents a step change in NET management, significantly improving survival. However, objective response to PRRT is approximately 20%, is poor. There are no predictive biomarkers of response. Uptake on 68Ga-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: We performed a phase I study to evaluate the safety and radiation dosimetry of the sstr2 antagonists 68Ga-DOTATATE and 177Lu-OPS201 (68Ga-DOTATATE and 177Lu-OPS201). This study was conducted in a phase I/II clinical trial of 68Ga-DOTATATE and 177Lu-OPS201. In patients with metastatic well differentiated NETs, 68Ga-DOTATATE was used to calculate tumor and normal organ radiation doses. Dosimetry was then calculated to administer 177Lu-OPS201 divided doses for the 2nd and 3rd fractions, 8-10 weeks apart.

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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 is, however, not yet 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 SREs were calculated. In patients experiencing an SRE within 1 month after diagnosis (i.e. before efficacy of ART could be assessed), TSSTRE 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% more than after 1 month. Median TSSTRE was 63.8 months with ART and 127.0 months without ART (p = 0.1751). TSSTRE 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). Of note, 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 TSSTRE 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 TSSTRE, no subgroup with a benefit of ART could be identified. The use of ART in NEN should be questioned and evaluated prospectively.
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: TGF-β1 signaling is associated with HCC progression. Inhibition of TGF-B 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 an 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 v4.0). 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, 81.8%; 18.2%; ethnicity: hepatitis C = 34.1%, hepatitis B = 18.2%, alcohol = 20.5%, multiple = 13.6%; AFP ≥200 μg/L = 50%; portal vein invasion = 34%. Incidence of AE was similar between G dose levels. Overall in the 150mg BID cohort, treatment related AEs (≥1%) 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 neutrophils (10.2%), and two pts on 150 mg BID reported a study drug related AE (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, survival (MOS) was 139 months with 61% 5-year OS. MOS was 53 months in patients with incurable HCC and no prior systemic therapy.

Conclusions: The combination of G plus S demonstrated acceptable safety and a meaningful OS of 17.9 months. Median OS was 17.9 (14.8, not estimable) months. Conclusions: 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: OS, progression-free survival (PFS), overall response rate (ORR) and safety were assessed. The primary endpoint was OS. OS, progression-free survival (PFS), overall response rate (ORR), and quality of life (QoL) were secondary endpoints. The study drug was rapidly absorbed and had an elimination half-life of approximately 8h. Median TTP (RECIST) was 4.1 (2.8, 5.5) months. OS, survival (MOS) was 139 months with 61% 5-year OS. MOS was 53 months in patients with incurable HCC and no prior systemic therapy. The primary endpoint was OS. In the 150 mg BID cohort, treatment related AEs (≥1%) 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 neutrophils (10.2%), and two pts on 150 mg BID reported a study drug related AE (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, survival (MOS) was 139 months with 61% 5-year OS. MOS was 53 months in patients with incurable HCC and no prior systemic therapy. The primary endpoint was OS. 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. Median OS was 17.9 (14.8, NE) months. Conclusions: 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.

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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 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-IV complications occurred in 21% with one 30-day postoperative death. 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 cancer (73 PMCA/77 DPAM). Conclusions: CRS/HIPEC is a potent 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.
**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. 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 15.6 months, 103/119 (87.0%) 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 6.95, 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: ACRIN126122000763842.

**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:** Eminet 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. Genomic tumor next generation sequencing (NGS) 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 genomic testing in all patients evaluated in MSKCCs Pancreatic Oncology (PO) clinic. We report on the past 3 years of NGS testing at MSKCC and the implications for therapy as well as for cancer predisposition in blood relatives. **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. Clinico-pathological features, time to progression on platinum (TPP) 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 60.6 years (range 29-81) compared to 66.8 years (range 18-69) without a GA. Median age at dx was 54.6 (33-88) for BRCA1 and 61 (37-77) for BRCA2 GA. 3/9 (33%) had a GA on dx < 50, 2/63 pts (3%) with no family hx had a GA (CONF 2A, PM212). N = 5/22 pts (23%) with a 1° degree relative (DR) with a GA had a GA. N = 13/45 pts (29%) had a GA with either a 1° or 2° DR with PAC. 19/84 pts (23%) with ≥2 2° DR with cancer had a GA detected. For median OS and TPP 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 TPP on platinum therapy (Table). **Conclusions:** GAs 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.

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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; NLR > 4 a value of 1, serum albumin > 4 g/dl assigned a value of 1; and serum albumin < 4 g/dl assigned a value of 0. 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 (p < 0.0005). 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.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Median OS (months)</th>
<th>Interquartile Range</th>
<th>Percent Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS 0 (n = 213)</td>
<td>14.7</td>
<td>8.5-26.3</td>
<td>22.1 (47)</td>
</tr>
<tr>
<td>MPS 1 (n = 332)</td>
<td>10.3</td>
<td>4.5-21.9</td>
<td>17.2 (57)</td>
</tr>
<tr>
<td>MPS 2 (n = 288)</td>
<td>6.2</td>
<td>4.3-14.8</td>
<td>13.1 (38)</td>
</tr>
<tr>
<td>Overall (n = 833)</td>
<td>10.2</td>
<td>4.4-21.5</td>
<td>17.0 (142)</td>
</tr>
</tbody>
</table>

**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 multicenter, single-arm phase II study. Patients with BRPC received S-1 (40 mg/m² 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 < 180°; or (3) tumor contact with common hepatic artery or celiac axis < 180°. Primary endpoint was R0 resection rate in BRPC confirmed by central review. At least 40 patients were required, with one-sided α = 0.05 and β = 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/curative resection. Of the 28 resections conducted in 27, and R1 and R2 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.

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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).

**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 vs Gem showed that the addition of nab-P reduced progressive disease (PD) and death (death) compared to Gem alone (Gem).

**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 variable analysis or considered clinically important (stepwise selection to remain in model).

**Predictors:** 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.

**Tables:**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Weight (c-index)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPS (per 10-unit increase)</td>
<td>0.94</td>
<td>0.92-0.95</td>
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<tr>
<td>Presence of liver metastasis</td>
<td>1.62</td>
<td>1.29-2.03</td>
</tr>
</tbody>
</table>

**Conclusion:** A nomogram was internally validated using bootstrapping, a variable selection or considered clinically important. 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 variable selection or considered clinically important. 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 variable selection or considered clinically important.
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 Flaim, Christie NHS Foundation Trust, Manchester, United Kingdom

Background: Adjuvant chemotherapy following PC resection improves overall survival (OS), but 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 non-significant but non-significant greater effect of adjuvant therapy in pts with N0 R0 (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 repair (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. Cytotoxicity 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 regimes. 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/Abaxanxe at MDACC from 1/2010-1/2013. Families defined as 1st through 3rd generation relatives with 1 or more family members with pancreatic 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 the presence of BRCA1, BRCA2, PALB2, and PALB2 Results: Average age was 61. 60% of patients were male. We sequenced blood and tissue samples where available. We found at least 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 PALB2. Among the subset of patients with possible deleterious mutations, there were trends towards improved survival in pts with BRCA or PALB2 aberrations (3074 vs 2717, p = ns) but worse outcomes in those with MMR gene defects (1813 vs 3874, p = .126). Table 1 indicates outcomes based on number of family members with cancer with their associated risk and 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.

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 MMR gene, ATM or PALB2 results for 4,925 patients with PC to generate 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 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.
Phase II study of autophagy inhibition with hydroxycloroquine (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, Massachusetts

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 2012/11-9/2016 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 (c = 1-10235), femoral 24 mm (max). Gr 3 toxicity was noted in 2/4 (pm) pts (nausea, 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 improve DFS. Further pathologic/correlative studies, particularly in outstanding pathologic responders and long term survivors are ongoing. Clinical trial information: NCT01494155.

A phase Vii 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 58-80% 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, immunologic 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 for 6 cycles). Thereafter TG01/GM-CSF were given 4-weekly up to 1 yr and 12-weekly up to 2 yr. 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 death. 16/19 (84%) pts had a positive DTH by week 11. Proliferation of mutant RAS specific T-cells is being analysed. 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 adjuvant 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.
Effect of nutritional and nutritional (IN) status on induction chemotherapy (CT) followed by chemoradiation therapy (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 from either treatment. IN statuses defined by specific C-reactive protein (CRP) and serum albumin (Alb) were 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 = 151/49 in Arm A/B). Glasgow Prognostic Score (GPS) was classified by baseline CRP and Alb. Pts with a CRP > 10 mg/L and Alb < 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. Those on 22 enrolled pts, an 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 2.12 (82-2.23) and 0.59 (0.34-3.4) in the OS (GPS 0/1/2) and GPS 1/2 group (n = 7/15) (Interaction = 0.02). HRs were 2.57 (1.36-4.86) and 0.70 (0.37-1.32) in the low CRP group (≤ 1.35 mg/L, n = 25/25) and high CRP (> 1.35 mg/L, n = 26/26) (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 (≤ 0.7 mg/L, n = 16/16), 2nd ( > 0.7, ≤ 3.0 mg/L, n = 20/16), and 3rd tertary CRP group ( > 3.0 mg/L, n = 19/17) (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 (≤ 40 g/L, n = 28/26) (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 from induction CT followed by CRT for LAPC. Clinical trial information: UMIN000006811.

Molecular profiling of advanced pancreatic cancer (PC) patients from a phase II/I 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 (NCCT01064622; Catenacci et al. JCO 2015). Eligible patients had unrespectable PC and no prior therapy for metastatic disease. Patients samples (< 3ml) collected pre-treatment and at regular intervals and stored for –6–8 years were analyzed using InVision (enhanced taged-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 one patient each. An update on the analyses will be presented. 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.
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 was 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 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 prominent in later lines, but conclusions are restricted by limited pt numbers. Clinical decision making.

Characteristics and outcomes of resected pancreatic cystadenocarcinoma: A retrospective analysis of 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=7,077) from TCGA. Cox models were 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 differentiated 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 >4 cm: 17.5%, 24.3%, 53.5% vs. 16.8%, 48.3% and 32.1%, respectively, p < 0.0001); had 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. 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.

Gastrointestinal (Noncolorectal) Cancer

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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

**Methods:** 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 (PD-1), has demonstrated encouraging clinical activity in patients with advanced GC. These data support the rationale that combination nivolumab in combination with other IO agents or IO-centered 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-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 endpoint is objective response rate (ORR) 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.

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, NHMRI 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 (VEGFR-1, -2, -3), 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 (NHMR C 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 resistant following second line CT, will receive best supportive care plus 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 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/E COG, Alliance, and NRG) and the National Clinical Trials Network. Enrollment began in November 2015. Support: U10CA180821, U10CA180862; Clinical Trial Information: NCT02485834.

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 (1:1) to GS-5745 plus mFOLFOX6 plus placebo. Stratification factors include ECOG status (0 vs 1), geographic region (Latin America vs all other countries), and primary tumor site (gastric vs 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 cycle until disease progression. The primary endpoint is OS, and secondary endpoints include PFS, ORR, 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 EQ-5D-5L, and progression free survival and surgical mortality and morbidity. Recruitment has already started; currently (Feb 2017) 21 patients have been enrolled. EudraCT: 2014-002665-30. Clinical trial information: NCT02578368.

The Institute and Tennessee Oncology, PLLC, Nashville, TN

Background: Advanced cholangiocarcinoma (CC) is a life-threatening disease for which there are limited therapeutic options. Mutations in isocitrate dehydrogenase 1 (IDH1) occur in up to 25% of intrahepatic CC cases, miIDH1 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 miIDH1 enzyme, and is being tested in a phase 1 study that enrolled 73 patients (pts) with miIDH1 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 (N = 4) had a confirmed partial response and 56% (N = 6) 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 miIDH1 CC described here. Methods: ClarIDHy is a global, phase 3, multicenter, double-blind study randomizing 186 pts with miIDH1 CC in a 2:1 ratio to AG-120 (500 mg QD) or matched placebo (NCT029898857). Key eligibility criteria: nonresectable or metastatic CC; documented miIDH1 based on central laboratory testing; ECOG 0–1; measurable disease (RECIST v1.1); documented disease progression following ≤2 prior systemic therapies in the advanced setting, including at least 1 gemcitabine- or 5-fluorouracil-containing regimen; no prior miIDH1 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.
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 vs BSC vs placebo in 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 treatment approach (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 2:1:1 to receive pembro 200 mg IV QW + BSC or placebo QW + 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 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.

Gastrointestinal (Non colorectal) Cancer

TPS4144 Poster Session (Board #129a), 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, N0-1, M0) (7th UICC classification), 2) histologically confirmed aden (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/m² twice daily for 4 weeks. The primary endpoints will be OS. 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-sided 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.
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: GC is characterized by multiple DNA repair defects, including BRCA1/2, and other homologous recombination (HR) genes such as FANC, ATM, ATR (Waddell N, Nature 2015). Follicid 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 (Berger 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 D1-3 in 14-day cycles, and 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 BROCA/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 0.7-9 mos, 312 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.

CanStem111P trial: A phase III study of nab-paclitaxel (nab-PTX) with gemcitabine (gem) in adult patients with metastatic pancreatic ductal 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. Nab-paclitaxel is a first-in-class cancer stemness inhibitor identified by its ability to inhibit STAT3-driven gene transcription and sprenogenesis of cancer stem cells (Li et al, PNAS 112(26):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 (12+ 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 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 nab-paclitaxel 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 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.

TPS4147 Poster Session (Board #131a), 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 (mPDAC). 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 tumour microenvironment in PDAC. GEM and Nab-P induce PD-L1 expression, which may deplete-Strim in CAF 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 NCT02973918) 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 (150 mg/m^2 D1 q 28 days) in 4 cycles (75 mg D1, 8, 15) 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, 31 pts have been enrolled and the initial safety analysis is ongoing. Clinical trial information: NCT02879318.

TPS4148 Poster Session (Board #131b), Sat, 8:00 AM-11:30 AM

TPS4149 Poster Session (Board #132a), Sat, 8:00 AM-11:30 AM

TPS4150 Poster Session (Board #132b), Sat, 8:00 AM-11:30 AM
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 FOLFOXIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², 5-fluorouracil 2400 mg/m² for 4 cycles) or to 7 cycles of modified FOLFOXIRINOX 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/m², leucovorin 400 mg/m² and infusional 5-fluorouracil 2400 mg/m² 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 RO 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 mFOLFOXIRINOX 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 (PDAC) 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 (FOLFOXIRINOX, 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 PDAC, 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 of the portal or superior mesenteric veins; patent portal vein/splenic vein confluence; no metastases. Treatment includes 12 weeks [either 6 doses of mFOLFOXIRINOX (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 60% 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/NCCT 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

Methods: This is an investigator initiated, phaseIII, multicenter, double-blind, randomized trial comparing S-1 in combination with TLP0-001 or placebo for the patients with advanced pancreatic cancer refractory to standard chemotherapy. Patients are allocated to either DC vaccine (TLP0-001) or placebo for the patients with advanced pancreatic cancer refractory to standard chemotherapy. Exclusion: those off chemotherapy or gemcitabine/abraxane based-chemotherapy. This is a randomized, double-blind, placebo-controlled trial assessing safety, primary endpoint is progression-free survival, and secondary endpoints include OS, response rate, quality of life, and toxicity. The patients were enrolled from September 2016 to July 2017. Cancer Immunol Immunother, 2014 / Mayanagi et al Cancer Sci, 2015). TLP0-001 is active Dendritic cells loaded with epitope peptides derived from WT-1. The TLP0-001 + S-1 group received four cycles of TLP0-001 + S-1 and S-1 for 1 year. The TLP0-001 + S-1 group received four cycles of TLP0-001 + S-1 and S-1 for 1 year. The primary endpoint is progression-free survival (PFS), and secondary endpoints include OS, response rate, quality of life, and toxicity. The patients were enrolled from September 2016 to July 2017. Cancer Immunol Immunother, 2014 / Mayanagi et al Cancer Sci, 2015). TLP0-001 is active Dendritic cells loaded with epitope peptides derived from WT-1.

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 pancreatic cancer (LAPC). First Author: Valerie Lee, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Methods: 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 pancreatic cancer, but may be primed by SBRT via abscessal 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 resectable LAPC, predominant adenocarcinoma at diagnosis, with ECOG 0-1, who remain metastases free after 4-8 cycles of FOLFIRINOX or gemcitabine/nab-paclitaxel, induction therapy with ECOG 0-1. The pts were randomized to 1 cycle of cyclophosphamide, pembrolizumab, and GVAX for six cycles, or to 2 cycles of cyclophosphamide, pembrolizumab, and GVAX for six cycles, or to 2 cycles of cyclophosphamide, pembrolizumab, and GVAX for six cycles. The pts were then monitored for two years. The primary endpoint is DMFS. Secondary endpoints include overall survival, surgical resectability, pathological response, quality of life, and toxicology. 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 pathological quality control, tumors were analyzed for DNA copy number variants, somatic mutations (WES), DNA methylation, miRNA, non-coding RNA (lncRNA and miRNA) and (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_CV), increased from 32 in the original report. We identified 5 mutation signatures including APOBEC-a and b, ERC2C, 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 0.0078). The previously identified four miRNA 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 different clinical and epithelial-mesenchymal transition scores, carcinoïd-like signatures, 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 different treatment approaches.

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, ≥30-<60 mL/min, grade ≥2 neuropathy/ hearing loss, NYHA Class 3 heart failure), advanced UC, and no prior systemic therapy. Pts received pembro 200 mg Q3W. Imaging was performed at tumor sites and non-tumor sites after ≥6 mo of pembro. The phase II/III study of E+P in pts with advanced UC was an open-label, phase I/II study of E+P eligible UC patients. The non-inferiority 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 scoring approach (CPS) with ORR were evaluated. Results: As of the Dec 19, 2016, data cutoff, ORR was 29% (95% CI, 23-36); 35% (7%) and 81 (22%) pts achieved complete and partial responses. Another 69 (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 25% of all pts and were evaluable. ORR in the 110 pts with CPS ≥10% was 47% (95% CI, 38-57). Conclusions: Results confirm 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. Pembrolizumab 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: NCT02335424.
A phase III 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, Cannon Cancer 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 is presented the given 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. The most common non-hematologic toxicities (DLT) occurring in cohort C in pts receiving PAZ/PEM; updated DLTs in all cohorts are reported in Table. No Q3/4 ALT/AST elevations were reported in cohort C and patients receiving PAZ/PEM were dose-escalated in 70% and 60% in cohorts A and B, respectively. Best overall responses (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 → 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: NCT02493751.
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-IIl pts (Rini et al., Lancet Oncol 2015;16:676-85). We present further verification 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 HR 0.192; DFS HR 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

<table>
<thead>
<tr>
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<th>PBO, n = 90</th>
<th>SU, n = 103</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>TTR*</td>
<td>4.24 (2.31–7.80)</td>
<td>&lt;0.001</td>
<td>2.53 (1.29–4.97)</td>
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<tr>
<td>DFS</td>
<td>3.75 (2.13–6.60)</td>
<td>&lt;0.001</td>
<td>2.31 (1.20–4.43)</td>
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<td>High vs low RS group, n</td>
<td>48 vs 16</td>
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<tr>
<td>TTR*</td>
<td>9.18 (2.15–39.24)</td>
<td>&lt;0.001</td>
<td>1.86 (0.85-5.06)</td>
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<td>DFS</td>
<td>5.17 (1.78–14.99)</td>
<td>&lt;0.001</td>
<td>1.87 (0.67-5.07)</td>
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* HR (95% CI), p-value, per 25-units increase of RS * HR (95% CI), p-value, high vs low RS group.

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 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, and inherited cancer syndrome, were prospectively enrolled from medical oncology clinics and urology clinics to a germline 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 (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 pts. P-LP mutations were present in 29% of pts with R-P/UC primaries and 18% of pts with B primaries. 12 DNA damage response gene alterations were found (4 BRCA1, 2 BRCA2, 2 CHEK2, 1 ATM, 1 PIK3CA, 1 PNKC1, 1 NBN). Other alterations include 3 APC, 1 ATM, 1 BARD1, 1 FH, 1 FAP, 1 MSH6, 1 MLH1. Other mutations include 2 TP53, 1 PTEN, 1 PMS2, 1 TGFBR2, 1 TP53, 1 FH. Notably 3 pts had 2 alterations each (MSH6/ATR, BRCA2/ATR, BRCA1/BRCA2). 9/22 pts with P-LP mutations did not meet American College of Medical Genetics criteria for genetic counseling. 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 exome capture assay and genomic interrogation of microsatellite (MSI) 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 p=.004. 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, 95% CI 0.003, indicating that the effect of DDR alts is 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

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<td></td>
<td>Female 10 (36)</td>
<td>13 (47)</td>
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<td>nivolumab 7 (25)</td>
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<tr>
<td>Plt-free interval, months</td>
<td>Median (range)</td>
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<td>13 (54.2)</td>
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<tr>
<td>Deleterious DDR</td>
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<td>18 (75)</td>
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**4512** 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 (95% CI 1.05-2.43), p = 0.033, 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-chemotherapy amplifications in cell-cycle genes (CCNE3, cIAP1), cULL-5, FBXW7, and amplification of immune checkpoint genes (PD-L1/2).

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.

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**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 carcinoma. First Author: Eric Jonasch, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (95% CI 1.09-2.20), p = 0.052). The total number of inferred tumor subclones in pre- and post-treatment tumors was only borderline statistically worse overall survival (HRR 1.86 [95% CI 1.12-3.06], p = 0.02), whereas pre-treatment proportion of subclonal mutations was associated with worse overall survival (HRR 1.38 [95% CI 1.13-2.06], p = 0.041) but not post-treatment proportion of subclonal mutations.

Conclusions: The majority of SUNITINIB patients receiving a TKI. Clinical trial information: NCT01499121.

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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Phase II study of pazopanib in patients with von Hippel-Lindau disease. First Author: Erik Jonash, 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 multitoxin inhibitor pazopanib to test this hypothesis. Methods: After obtaining IRB approval, patients with clinical features or genetic confirmation of VHL disease. Clinical trial information: NCT01436227.

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Expression status. The primary endpoint was overall response rate using incorporating intensity of staining. Pts were eligible irrespective of PD-L1 PD-L1 on tumor infiltrating immune cells using PD-L1 (22C3) assay was at least 1 salvage regimen (HDCT or SDCT) were eligible. Centrally assessed GCT who progressed after first line cisplatin-based chemotherapy and after disease had continued rising AFP level despite radiographic stability; both had progression of disease as their best response. The 2 pts with stable pembrolizumab doses was 2 (range, 1-8). There were 5 grade 3 adverse.

Results: Median AFP 615 (range, 1-32,760) and hCG 4 (range, 0.6-37,096). had non-seminoma. Primary tumor site was testis in 11 pts and mediastinum – 1.1 months. Median age at diagnosis was 41 (range 19 – 69) years. The primary tumor was gonadial 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 – 14.1 cm) main located 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 (> 2year). 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. All 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.

Assocationon treatment plasma HGF levels with overall survival (OS) in patients (pts) with advanced renal cell carcinoma (RCC) treated with interferon alpha (IFN) +/- 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 clinical outcomes. We assessed baseline plasma analyzed baseline ETDA 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 (KM) and 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<0.053). Conclusions: In addition to 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 pts continue to have high levels on treatment and are associated with a worse OS, suggesting that, HGF predicts for thera
tenfubrinated immune cells using PD-L1 (22C3) assay was at least 1 salvage regimen (HDCT or SDCT) were eligible. Centrally assessed GCT who progressed after first line cisplatin-based chemotherapy and after disease had continued rising AFP level despite radiographic stability; both had progression of disease as their best response. The 2 pts with stable 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. All 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.

Association of on-treatment plasma HGF levels with overall survival (OS) in patients (pts) with advanced renal cell carcinoma (RCC) treated with interferon alpha (IFN) +/- 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 clinical outcomes. We assessed baseline plasma

Results: Median AFP 615 (range, 1-32,760) and hCG 4 (range, 0.6-37,096). had non-seminoma. Primary tumor site was testis in 11 pts and mediastinum – 1.1 months. Median age at diagnosis was 41 (range 19 – 69) years. The primary tumor was gonadial 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 – 14.1 cm) main located 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 (> 2year). 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. All 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.

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. Sorafenib 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 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 PBRM1mutations 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 multivari- ate 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 be 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.
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 underestimation (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), unsampled 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 yds at diagnosis), 9% had a familiar history of RCC, 6% multiloc 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, famly history, multiloc 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, SDHD, FH). Prevalence of CHEK2 mts was compared to population databases (ExAC): CHEK2 conferred a relative risk of 10.9 (<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 mts were not identified using standard clinical screening rationale for broad testing. Once the increased risk is confirmed, CHEK2 should be included in RCC genetic testing.

![Table](https://example.com/table.png)

*2 pts with BAP1 had both ccRCC and nccRCC; **1 pt with CHEK2 had both ccRCC and nccRCC

4526 Posterior Discussion Session; Displayed in 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). Qianonarios were completed at baseline and every 8 weeks thereafter. 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 (<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; dyspea; insomnia; appetite loss; constipation; and diarrhea were observed at ≥1 time points. With the exception of cognitive functioning, no significant worsening in subscale scores of any of the EORTC QLQ-C30 subscales 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 tar-score 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.
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 2 pts with mUC from JAVELIN Solid Tumor (NCT01772004) and further characterize the clinical activity of avelumab in this disease. Methods: Pts with mUC progressing 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 92.4% (95% CI 71.5–98.0). 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 ≥3 in 2.4%). There was 1 treatment-related death (pneumonitis).

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Conclusions: Occurred in 11% and 6% of pts, respectively. Investigator-assessed RECIST v1.1 increased appetite and anemia. TRAEs leading to dose interruption or discontinuation included fatigue, diarrhea, and rash. 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. None led to death. TRAEs leading to dose interruption or discontinuation occurred in 11% and 6% of pts, respectively.

Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>Female</th>
<th>p-value</th>
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<tr>
<td>Median age (range)</td>
<td>70 (60-80)</td>
<td>70 (60-80)</td>
<td>0.38</td>
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<tr>
<td>Primary tumor</td>
<td>34%</td>
<td>36%</td>
<td>0.52</td>
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<tr>
<td>Bladder</td>
<td>78%</td>
<td>78%</td>
<td>0.99</td>
</tr>
<tr>
<td>Urethra</td>
<td>18%</td>
<td>18%</td>
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<tr>
<td>Other</td>
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<td>4%</td>
<td>0.99</td>
</tr>
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<td>NRG1</td>
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<td>9%</td>
<td>0.99</td>
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<td>66% (25%)</td>
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</tr>
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<td>2%</td>
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<tr>
<td>Prior cystectomy</td>
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</tr>
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</table>

Note: *Other*: 4% | n = 202 evaluable; n = 71/13 pts evaluable; n = 218

4532 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 chemotherapeutic regimens. Atezolizumab (atezo; PD-L1) was approved in the US for mUC in the post-platinum setting. Here we report the preliminary efficacy results from an expanded access program conducted to grant access to aezo, prior to commercial availability, to a broader range of mUC pts than are typically eligible for Phase III trials.

Methods: From November 2015-August 2017, this study (NCT02589717) enrolled mUC pts who progressed following or during platinum. Atezolizumab (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 visit.

Results: 218 pts were enrolled at 36 sites in the US, with 214 treated pts comprising the safety/efficacy population (Table 1). 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. None led to death. 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, aezo was administered to ≥ 200 mUC pts. Aezo was overall safe and tolerable, supporting its use in a wider platinum-based population. Clinical trial results have shown aezo to be an effective and tolerable therapy in advanced mUC patients.

4533 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 sampling 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 captured-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 for whom cfDNA identified new mutations in 50% (9/18) of pts for whom cfDNA identified somatic mutations and tissue NGS was not attempted. Conclusions: NGS of cfDNA from mUC pts is feasible and successfully detected actionable alterations when tumor sequencing failed. The differences between tumor and cfDNA mutation profiles in many pts may reflect tumor evolution or intratumoral heterogeneity. Mutation profiles in cfDNA may be incomplete as compared with NGS of archival tissue, and further investigation of plasma cfDNA for genomic profiling is warranted.

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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 EU 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 administration of adjuvant 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. Conclusion: 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.

Effectiveness of the Moreau strain of Bacillus Calmette-Guerin (BCG) for nonmuscle invasive bladder cancer.

Methods: We retrospectively analyzed 336 consecutive patients, who received adjuvant intravesical instillation therapy with BCG Moreau 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. 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. Conclusion: BCG Moreau has been 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/m² 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; 9 pts randomized to D+B. Overall response rates were 15% (95% CI: 0.15-0.30), and 2 pts responded. In pts who progressed during lead-in, the median duration of response was 1.9 months. 1 pt discontinued tx due to AE (disseminated intravascular coagulation). N=5 pts had neutropenia (10.5%), decreased WBCs (10.5%), 2 pts had D dose reductions due to neutropenia. 2 pts had D dose reductions due to AE (neutropenia). Conclusions: Preliminary results show that B-701 combines safely and effectively w/ D in pts w/ UCC. 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.

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 prevalent genitourinary cancer in Pakistan. It is especially common in population that consumes smokeless tobacco. Advanced stage at diagnosis is usual presentation 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 in stage range from T2-3, NO and MO to be selected. The patients were planned for gemcitabine and cisplatinum (GC) every three weeks in a dose of 1000 mg/m² and 40 mg/m² on D1 and D8 of each cycle respectively. Ultrasoundography 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/m². 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 (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 hemato logical related grade I-2 toxicity. Four year DFS and OS were 43% and 52% respectively. Mean and median DFS (year) were 3.6 (95% CI 2.91 to 3.42) and 2.68 (95% CI 2.41 to 2.93) respectively. Mean and median OS (year) were 3.95 (95% CI 3.67 to 4.21) and 3.55 (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/m² q3 week for 6 cycles) versus best supportive care (BSC) in patients (pts) with histologically proven bladder cancer. All (N=17) FGFR3 mut/fus (N=5) patients were available for assessment. Results: 6 pts on each arm were evaluated for response after having 2/3 cycles; 1 pt on CAB during 1st stage (i.e. total of 20 pts randomised) and 4 pts on BSC (2 on CAB-B1 and 2 on BSC). Median OS was 5.6 months (95% confidence interval (CI) 1.34-7.6). Results of 0.20, 80% power, 5% alpha level). The trial was supported by grant from Astellas. Conclusions: CAB-B1 was a single centre phase II randomised controlled trial of Cabazitaxel (CAB; 25mg/m² q3 week for 6 cycles) versus best supportive care (BSC) in patients (pts) with histologically proven bladder cancer (pts who progressed after chemotherapy: Results of a phase II trial—CAB-B1. First Author: Anjali Zarkar, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom

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 ideal 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 ≥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 used mixed effects logistic regression models 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 (IC = 0.26). The model with patient factors showed good fit (AUC = 0.93, 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.

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Activity of RX-3117, an oral antimitabolite nucleoside, in subjects with metastatic bladder cancer resistant to gemcitabine: Preliminary results of a phase Ia/Ib study. First Author: Jun Gong, City of Hope Comprehensive Cancer Center, Duarte, CA

**Background:** RX-3117 is an oral small molecule antimitabolite, cyclopentyl pyrimidine 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 ≥ 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 cfDNA assessments showing increase of TPS3 alterations. Clinical benefit with RX-3117 was achieved in spite of increase 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 inhibitor. Activity persisted despite development of resistance in this subject identified by ctDNA. Clinical trial information: NCT02030067.

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Myeloid derived suppressor cells (MDSC) and inflammatory biomarkers in metastatic uterine cervical carcinoma (n=UC). First Author: Moshe Chaim Ornstein, Cleveland Clinic Taussig Cancer Institute, 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 nUC. 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 Lin(-), CD33(+)/HLA-DR(-) [(T)otal MDSC]. MDSC subsets were defined as (G)PBMC subsets. MDSCs were identified by flow cytometry in WB and defined as unfractionated whole blood (WB) and in peripheral blood mononuclear cells (PBMC). 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 (31-93), 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 = 0.05). Higher % WB I-MDSC correlated with lower blood neutrophil/lymphocyte ratio (NLR) (p = 0.009), while higher WB and PBMC %PBMC MDSC were associated with higher NLR (p = 0.03 and p = 0.02, respectively). Higher I-MDSC / G-MDSC ratio was associated with higher NLR (r = -0.35, p = 0.02) and with various clinicopathologic parameters. Conclusions: Higher I-MDSC / G-MDSC ratio inversely correlates with NLR, which is considered an inflammatory biomarker and had prognostic value in other studies. The mechanism of MDSC interaction with inflammatory response in nUC pts merits evaluation and is being investigated in a larger cohort of UC pts on chemotherapy or immunotherapy (with longer follow up).

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 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. χ² 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, 1,856 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 yrs (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 ≥ 5yr FUP, 25 pts 2-5yr FUP. The median latency of SM was 5.3yrs (IQR: 1.8-6.1) for hem SM and 6.6yrs (IQR: 1.2-10.8) for solid SM. Median FUP was 6.4yrs. Univariable, 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, highlighting the need for prospective studies. Our data are ongoing and we will compare the SM incidence from EBMT database with SM rates in the general EU population.

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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 (2-3) 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-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, adequate 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%), PR 11 (33.3%), SD 4 (12.5%), DCR 17 (51.5%). DFS of CR/NED: median 51 (8-105) months, of PR 42 (2-105) months, of SD 25 (2-105) months. OS Favourable Responders: 51 (6-105) months, OS responders: 25 (2-105) months, median followup 25 (2-105) months. Conclusions: Sequential HD-CTx with one or more cycles of 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.

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4556 Poster Session (Board #234), Sun, 8:00 AM-11:30 AM
Genetic 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 and/or clonality was predicted to be present in all cancer cells) within 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 metastatic tumors. Treatment of genomic concordance, particularly for mutations, is poor between primary and metastatic GCT samples. Clonal, cell-free DNA analysis may help overcome this limitation by also detecting alterations in progressing 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%, 95%CI 79.8-85.0; 21 complete responses, 68 partial responses and 51 SD). EPI-TAX was able to control disease in 56 (70.9%, 95%CI 61.0-80.0) out of 79 pts who were in progression. Beyer score after EPI-TAX resulted 0 in 70.6% of pts. Successful harvest of SC was achieved in 146 (85.8%, 95%CI 80.5-91.1) pts. EPI-TAX was well tolerated with peripheral neurotoxicity. Treatment of bone marrow toxicity 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 (0.5-233) the 2- and 10-years OS for the subgroup consolidation were 78.2% (95%CI 69.1-87.4) and 66.9% (95%CI 54.4-78.6). Disease control by EPI-TAX resulted 55.8% (95%CI 42.4-69.2) and 36.2% (95%CI 24.9-51.4) 2- and 10-years OS compared to 14.6% (95%CI 1.6-32.9) of pts 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 (PBSC) 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 group analysis suggested multimodality therapy improves survival probabilities in pts with brain mets at relapse (UCD.2016;1:3414; 345-51). We report our experience on managing 25 consecutive pts with testicular GCT who undergo retroperitoneal lymph node dissection (RPNLD) for residual masses 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. Clonal, cell-free DNA analysis may help overcome this limitation by also detecting alterations in progressing tumors without need for a new biopsy.

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 features from medical images. We aimed to assess if radiomics can predict pathology of post chemotherapy retroperitoneal masses in germ cell tumors. Methods: All pts with metastatic testicular GCT 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%, 95%CI 79.8-85.0; 21 complete responses, 68 partial responses and 51 SD). EPI-TAX was able to control disease in 56 (70.9%, 95%CI 61.0-80.0) out of 79 pts who were in progression. Beyer score after EPI-TAX resulted 0 in 70.6% of pts. Successful harvest of SC was achieved in 146 (85.8%, 95%CI 80.5-91.1) pts. EPI-TAX was well tolerated with peripheral neurotoxicity. Treatment of bone marrow toxicity 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 (0.5-233) the 2- and 10-years OS for the subgroup consolidation were 78.2% (95%CI 69.1-87.4) and 66.9% (95%CI 54.4-78.6). Disease control by EPI-TAX resulted 55.8% (95%CI 42.4-69.2) and 36.2% (95%CI 24.9-51.4) 2- and 10-years OS compared to 14.6% (95%CI 1.6-32.9) of pts 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.

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Results: 

assessed for overall response rate (ORR) q8wks (RECIST 1.1). Adverse expansion cohort of CaboNivo has initiated enrollment. Tumors were (CaboNivoIpi). Pts received Cabo PO daily and Nivo IV (part 1) with Ipi levels (DL) for part 1 (CaboNivo) and 18 pts were treated in 3 DL for part 2

A phase I study of cabozantinib plus nivolumab (CaboNivo) and cabonivo

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 pts with refractory metastatic (m) urothelial carcinoma (UC) and other genitourinary (GU) tumors. First Author: Andrea B. Apolo, Genitourinary Malignancies Branch, Center for Cancer Efficacy, 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 in part 2 (CaboNivoIpi). Pts received Cabo PO daily and Nivo IV (part 1) with (Ipi 1mg/kg x 4 doses 3qwks (part 2). A mUC and a renal cell carcinoma (RCC) expansion cohort of CaboNivo has initiated enrollment. Tumors were assessed for response (RECIST 1.1; ORR) and for disease control rate (DCR). Safety endpoints (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 30-77), 41 (85%) were male. Common treatment-related G1/2 AEs for CaboNivo: ALT increase (67%), fatigue (63%), diarrhea (60%), hyperlipidism (57%); CaboNivoIpi: fatigue (72%), diarrhea (61%), anorexia (61%); Grade 3 AEs for CaboNivo: hypertension (23%), neutropenia (17%), hyperphosphatemia (13%), lipase increase (10%), fatigue (7%), aseptic meningitis (7%); Grade 3 AEs for CaboNivoIpi: hyperphosphatemia (19%), hypertension (19%), fatigue (13%), hypernatremia (13%), nausea (13%), lipase increase (11%), colitis (6%); 4G 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 16% (mUC 29%). 11/13 (85%) 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 treatment. Here, patients treated with 3xEP had a non-inferior outcome. A baseline LDH < 2.0 UNL and a tumor marker decline after first treatment cycle can be used for further stratification.

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 morbidities. 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 ≥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 vs 2.3 (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 and an LDH ≤ 2.0 UNL and an adequate follow-up program may be further supported with e-health tools. Clinical trial information: NCT01783145.
Pazopanib exposure-response assessment as adjuvant therapy for patients with localized or locally advanced renal cell carcinoma (RCC) following nephrectomy. First Author: Cora N. Stemberg, San Camilo 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 grade 3/4 AEs, and treatment discontinuation due to hypotension 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 hypotension, which was adequately controlled and managed. Clinical trial information: NCT01235962.

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

**Methods:** Patients received 10 mg daily EVE or placebo for nine 6-week cycles. Trough levels were assessed at cycle 1 and 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 odds ratios were adjusted for 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. Results 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).

Efficacy and safety of peglated 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 cytotoxic T cell and proliferation of CD8+ T cells at higher concentrations. IL-10 receptors and PD1 are expressed on activated CD8 T cells and de-novo oligoclonal expansion of T cell clones in the blood. AM0010 in combination with nivolumab is well-tolerated in patients with advanced RCC, including anemia (9), thrombocytopenia (5), hypertiglyceremia (4). This study continued to demonstrate the efficacy of AM0010 in combination with nivolumab. Clinical trial information: NCT02009449.
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 Nx in the phase 3 METEOR trial (NCT01865747). Methods: 658 pts with clear cell RCC and ≥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. The primary endpoints were progression-free survival (PFS) and objective response rate (ORR). Results: 85% of enrolled pts had prior Nx of which 7% were partial; 15% had no prior nephrectomy (Nnx). Baseline characteristics, including Karnofsky performance status (KPS), MSKCC risk group, time from diagnosis to randomization, and median sum of diameters (SdD) for tumor lesions, were less favorable for the Nnx subgroup (Table). Improved PFS and OS with cabo vs eve were observed regardless of Nx status. For the Nnx 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 Nnx 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 Nnx 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 Nnx. 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.

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-1PD-L1 and MET receptors have clinical efficacy role, 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 specimens 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 tumors, 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 no discordance 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 (TC) and metastatic lesions (IC) with treated lavage lesions (TC) and metastases (IC) 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) in mRCC, PD-L1 and MET expression suggests that the assessment as predictive biomarkers may require analysis of metastatic lesions.

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 38% complete, 37.3% partial response, 33% stable, 25% 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 = 0.002), HR = 1.99 (95%CI 1,12-3.19). Three pts had > 3 CTCs. 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 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.

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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 favored PAZ in terms of 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 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 PAZ and SUN. Results: 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.

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**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 survivals 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 T effector cells, 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/mm²) 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+ and Foxp3+ cells in the IM and 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.

**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.

**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 Danskov, 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). HRs for OS also favored cabo (HR 0.72, 95% CI 0.53–0.95 for 65–74 years old; 0.53, 95% CI 0.37–0.77 for 75 years) are presented.

**Conclusions:** Median number of doses received was 10 (1–31) and 82 (21%) pts were treated beyond progression. Among 389 pts, 18 (5%) discontinued treatment due to AE. The best overall response rate was 17% including one complete and 66 partial responses, whereas 121 (31%) pts 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 of age, presence of brain or bone metastases and number of prior therapies. This study presents the most extensive reported real-world experience with nivolumab in pre-treated RCC pts. These first data seem to confirm efficacy and safety 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.

**Poster Session (Board #257), 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. 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 (5%) discontinued treatment due to AE. The best overall response rate was 17% including one complete and 66 partial responses, whereas 121 (31%) pts 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 of age, presence of brain or bone metastases. This study provides the most extensive reported real-world experience with nivolumab in pre-treated RCC pts. These first data seem to confirm efficacy and safety 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.

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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 carcinoma (mRCC) patient population, including geriatric patients. Methods: Using the IMDC database, a retrospective analysis was performed on mRCC patients treated with IO, as is 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 33% fourth-line treatment). Patients treated with second-line IO therapy were divided into favorable, intermediate, and poor risk using IMDC criteria; the corresponding median DOT rates were 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 patients into favorable, intermediate, and poor risk groups for DOT. Age may not be a factor influencing DOT.

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Association of circulating tumor DNA (ctDNA) detection in metastatic renal cell carcinoma (mRCC) with tumor burden. First Author: Manuel Cañito 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. Methods: Data was obtained from pts with radiographically confirmed stage IV RCC who received IO therapy. ctDNA was assessed by a qPCR assay. Detection was defined as the presence of circulating tumor DNA (ctDNA). Results: Of 224 pts, 89 (40%) had detectable ctDNA. Among pts with evaluable OS, the ORR to IO was 29% (95%CI 23-36). Median OS was 11.8 (95%CI 9.5-14.8) months in pts with detectable ctDNA vs. 7.5 (95%CI 6.7-8.4) months in pts without detectable ctDNA (p = 0.041). Furthermore, when evaluated as a continuous variable, number of mutations was associated with impaired homologous repair and increased non-homologous end joining (NHEJ). Conclusions: The presence of detectable ctDNA may be associated with worse OS and a mutator phenotype.

CTDNAs in metastatic renal cell carcinoma: Multi-trial meta-analysis. First Author: Andre Poisl Fay, PUCRS School of Medicine, Porto Alegre, Brazil

Background: 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 patients into favorable, intermediate, and poor risk groups for DOT. Age may not be a factor influencing DOT.

Clinical and molecular determinants that distinguish early and advanced stages of clear cell renal cell carcinoma (ccRCC). 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 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 PBRM1. We hypothesized that VHL loss leads to defective DDR as an early event in ccRCC carcinogenesis, giving way to a mutant 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 (RPTC) with VHL/SETD2 knockdown and in murine embryo fibroblasts (MEFs) from Vhl and Setd2 knockout mice treated with etoposide via qH2AX 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, and SETD2. WES revealed ~100 mutations in unique genes, which we hypothesized may have functional impact on the DDR. Conclusions: Genomic instability and DNA damage repair in clear cell renal cell carcinoma (cRCC) is due to the presence of VHL mutations. Analysis of a single, tumor-specific gene such as VHL may be insufficient for comprehensive DDR analysis.

CTDNAs in metastatic renal cell carcinoma: Multi-trial meta-analysis. First Author: Andre Poisl Fay, PUCRS School of Medicine, Porto Alegre, Brazil

Background: 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 patients into favorable, intermediate, and poor risk groups for DOT. Age may not be a factor influencing DOT.

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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 Posil 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 to other regions. Highest OS was observed in Asia/Oceania (A/OA), and Eastern Europe (EE). OS differed among patients enrolled on trials in the US compared to Western Europe (20.3 vs. 17.4 months, respectively; HR: 1.15; 95%CI 1.03-1.3 p = 0.019). All grade treatment-related adverse events (AE) were reported more frequently in US. There were no significant differences in grade 3-5 AEs between groups. Conclusions: We highlight that despite differing baseline characteristics, OS is similar among most geographic regions. Factors such as disease biology, access to care, AE reporting, and quality of care may contribute to similar outcomes in different regions among patients who may be further characterized.
Background: In a phase III study (NCT00083889), treatment-naive patients (pts) with metastatic renal cell carcinoma (mRCC) of all prognostic risk groups were treated with sunitinib or interferon-α (IFNα). 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 (9.7–13.8) vs 8.5 (6.5–10.7) mo, and mOS (95% CI) was 28.2 (23.0–not estimable) vs 16.3 (13.3–19.4) 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.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Favorable risk (n=134)</th>
<th>Intermediate risk (n=205)</th>
<th>Poor risk (n=34)</th>
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<tr>
<td>ORR, %</td>
<td>58.2</td>
<td>42.4</td>
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<tr>
<td>(95% CI)</td>
<td>(49.4–66.7)</td>
<td>(35.8–49.7)</td>
<td>(6.8–34.5)</td>
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<tr>
<td>PFS, mo</td>
<td>16.0</td>
<td>10.7</td>
<td>2.5</td>
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<tr>
<td>(95% CI)</td>
<td>(13.3–17.3)</td>
<td>(6.8–12.5)</td>
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<tr>
<td>OS HR, mo (vs IFN-α; 95% CI)</td>
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<td>0.47 (0.30–0.69)</td>
<td>0.91 (0.54–1.54)</td>
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<td>OL, mo (vs IMDC, 95% CI)</td>
<td>NE (NE–NE)</td>
<td>23.0</td>
<td>1.05 (0.66–1.67)</td>
</tr>
<tr>
<td>OS HR, mo (vs IFN-α; 95% CI)</td>
<td>NE (NE–NE)</td>
<td>23.0</td>
<td>1.05 (0.66–1.67)</td>
</tr>
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</table>

HR=hazard ratio; NE=not estimable

Conclusion: 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 improve 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.

<table>
<thead>
<tr>
<th>Correlation</th>
<th>No. of units</th>
<th>R-square</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation between 5 yr OS and DFS</td>
<td>22*</td>
<td>0.49</td>
<td>0.15-0.68</td>
</tr>
<tr>
<td>Correlation between DFS and OS treatment effects (HR)**</td>
<td>11</td>
<td>0.44</td>
<td>0.00-0.69</td>
</tr>
</tbody>
</table>

*11 (trials) * 2 (arms) = 22 units **Natural log transformed
Incidence of T3a upstaging and survival after partial nephrectomy: Size-stratified rates and implications for prognosis. First Author: Anurav 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 undergone 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 >7–9cm (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 upstaging 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 than increasing tumor size, reinforcing the need for improvements in identifying patients at risk of up-staging.

TPS4590 Poster Session (Board #268a), 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: Anurav 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 undergone 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 >7–9cm (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 upstaging 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 than increasing tumor size, reinforcing the need for improvements in identifying patients at risk of up-staging.

TPS4591 Poster Session (Board #268a), 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: Anurav 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 undergone 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 >7–9cm (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 upstaging 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 than increasing tumor size, reinforcing the need for improvements in identifying patients at risk of up-staging.
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. Grimmson, 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 1 (n = 150) is complete response rate (CR), 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 CRs 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 assessed at 30-day safety assessment or 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 in 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.

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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 carcinoma. 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 an 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 α = 0.05 and β = 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 has been slower than expected, but the current accrual rate is about 6-7 patients a month. We invite institutions and collaborative 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 Oncol 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 ≤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 sex (males vs females) and region (US vs rest of the world). Pts receive either avelumab 10 mg/kg IV Q2W + axitinib 5 mg orally twice daily (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 ≥18 years with confirmed advanced RCC diagnosis, ≥ 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, Karnofsky Performance Status ≥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 rates, progression-free 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 analyses is planned for efficacy or futility. Enrollment of 753 pts is planned to achieve a 5% power at 2-sided α = 0.05 to detect a difference in ≥ 1 of the primary comparisons. Clinical trial information: NCT028211861.
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-PD1 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. Another 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 MO RCC, we propose a three-pronged, multidisciplinary approach of pre-surgical 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 unparallelled correlative science in this global, randomized, unblinded, phase 3 National Clinical Trials Network study, 766 pts with clinical stage =T2 or any node positive MO 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.

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.

Methods: Eligible pts have PRCC (type I, type II, or NOS), Zubrod performance status 0-1, measurable disease (RECIST v1.1), central review and overall survival between treatment arms. Secondary end points include the comparison of survival, duration of response, disease control rate, safety, and patient-reported outcomes between arms. Enrollment is ongoing. Clinical trial information: NCT02853331.
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 Institute, Cleveland, OH

**Background:** Tivozanib is a biologically 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, multi-national, 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 receive CN 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 objectives to 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; ≥ 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 15% 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 Eidelbast 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-center cohort (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 Decision 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 0.80-0.89) 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, respectively. 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 genomic 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 (tx), 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: BRCA1, BRCA2, AT, 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. Mts 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 (> vs < 87%) vs wild type (58%, 39%; p = 0.013, 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). Contrasting 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.

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 STAM-PEDE (NCT00268476). First Author: Nicholas D. James, Queen Elizabeth Hospital, Coventry, United Kingdom.

Background: Abiraterone + prednisone (Abi) +/- veliparib (Vel) for patients (pts) with metastatic castration-resistant prostate cancer (CRPC): NCI 9012 updated clinical and genomic data. First Author: Maha Hussain, Northwestern University Robert H. Lurie Comprehensive Cancer Center, Chicago, IL.

Methods: Six pts were randomized to Arm A and 6 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. Mts 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 (> vs < 87%) vs wild type (58%, 39%; p = 0.013, 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). Contrasting 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.

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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: Gerard 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) in men with chemotherapy-naive mCRPC. 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 (P) 1 men, with chemotherapy-naive 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: ENZA + abi/P vs PBO + abi/P after PSA progression on ENZA.

**Results:** Median treatment duration in P2 was 5.6 mo for both arms. PFS event by radiographic/c/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 TTP 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 PFS 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%), and nausea (17% vs 9%), and fatigue (14% vs 15%). 

**Conclusions:** ENZA + abi/P plus PFS progression on ENZA was associated with increased hypoaldosteronism and nausea and did not result in a statistically significant improvement in composite PFS. The signal seen in PFS needs further evaluation. Clinical trial information: NCT01995513.

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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 (mCRPC). 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 bone scan index (aBSI), which quantifies the percent of skeletal mass involved by cancer. We aimed to extend the prognostic validation on a larger 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 = 225). The phase 3 trial was initiated and enrolled men 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® v.2 software and were blindly associated with outcomes. Baseline aBSI was evaluated for its prognostic independent association with overall survival (OS), radiographic progression-free survival (rPFS), and symptomatic skeletal related events (SSR). 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 to 1.3 mo (Q4) (P < 0.0001). Baseline aBSI was significantly associated with OS (HR 1.2 per doubling of BS; 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 = 0.000). Conclusions: This analysis represents the first phase 3 evaluation of aBSI as a clinically validated prognostic biomarker for OS, rPFS, and SSSE in men with bone-metastatic CRPC and provides independent prognostic information over commonly measured clinical characteristics. Clinical trial information: NCT01234311.

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5007 Oral Abstract Session, Sat, 1:15 PM-4:15 PM
Circulating tumor cell (CTC) number as a response endpoint in metastatic castration-resistant prostate cancer (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. Patients with missing values at week 13 were considered non-responders. The endpoints considered are shown in Table 1. Results: The dis- creminatory strength of the response endpoints with respect to OS was estimated using the weighted c-indices from the 5 studies were 0.67 (95% CI, 0.55 - 0.79) for CTC and 0.69 (95% CI, 0.62 - 0.76) for PSA. Conclusions: CTC and conversion endpoints had the highest dis- creminatory power for OS relative to the % decline in CTC or PSA endpoints. The percent of pts eligible and evaluable for the CTC endpoint was significantly higher than the conversion endpoint, 75% vs. 51%, respectively. Two absolute measures of CTC may be considered meaningful response indicators in mCRPC clinical trials.
Duration of androgen deprivation therapy in high risk prostate cancer: Final results of a randomized phase III trial. First Author, Abdouen Nabi, 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, 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 = 0.8412) with a global hazard ratio (HR) of 1.024 (95% CI 0.813-1.289, p = 0.8411). 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.

Conclusion: 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.

5008 Oral Abstract Session, Sat, 1:15 PM-4:15 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 genomic 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 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, 28.8% (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% (6/586) had germline only DDR mutatations, including 8 pts with two germline DDR mutations and 7 pts with two somatic DDR mutations (all BRCA2). Prostate cancer patients 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.

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 alleles). 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 BRCA2. 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 to only 14.9% of those with scores ≤6, 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

Whole exome sequencing (WES) of circulating tumor DNA (ctDNA) in patients with neuroendocrine prostate carcinoma (NEPC) informs tumor heterogeneity. First Author: Himisha Belin, 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 (Belin 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 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 = 0.0011) 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 tumor 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 adenocarcinoma development) of 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.

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

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The benefit of combining docetaxel to androgen deprivation therapy in localized and metastatic castration-sensitive prostate cancer as predicted by the PROpel trial: an analysis of two GETUG phase III trials. First Author: Shanna Rajjar, Institut Gustave Roussy, Villejuif, France

Background: Combining docetaxel to androgen deprivation therapy (ADT) improves survival in metastatic castration-sensitive prostate cancer (mCSPC) (Valle 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 present in 88/191 (46%) and 108/194 (56%) pts 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.

Conclusions: 

1. Docetaxel-related benefit in men with CSPC is predicted by ERG expression. This biomarker may help better select pts for docetaxel treatment.

2. Docetaxel-related benefit in men with mCRPC is predicted by ERG+ expression. This biomarker may help better select pts for docetaxel treatment.

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 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 hyper-methylation in >99% prostate cancers. Detection of circulating mGSTP1 DNA is a new marker that predicts response to docetaxel and overall survival (OS) in phase III trials involving metastatic prostate cancer (mCRPC).

Methods: The phase III SYNERGY study tested DTX +/- custirsen as 1st line chemotherapy in 88/191 (46%) and 33/79 (42%) pts with available tissue respectively in GETUG 12 and GETUG 15. ERG staining was present in 88/191 (46%) and 108/194 (56%) pts 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 present in 88/191 (46%) and 108/194 (56%) pts 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.

Conclusions: 

1. Docetaxel-related benefit in men with CSPC is predicted by ERG expression. This biomarker may help better select pts for docetaxel treatment.

2. Docetaxel-related benefit in men with mCRPC is predicted by ERG+ expression. This biomarker may help better select pts for docetaxel treatment.

Clinical trial information: NCT01505868.

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 OCU-4A-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 baseline (BL) to favorable OS (FOS) in phase II/III mCRPC is the foundation for a therapeutically relevant classification of prostate cancer. Clinical trial information: NCT00636960.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Conclusions: 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 PSAas 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 (PSA50) to BAT and PSA50 to enza re-challenge. The null hypothesis was a PSA50 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 same objective response rates in chemotherapy-naive mCRPC. Further prospective randomized studies are warranted. Clinical trial information: NCT02288936.

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: Mahé 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 cT1-4 N0 PC with post RP PSA ≥ 10 ng/ml + bx GS 6-10. A high risk factors defined as Gleason sum (GS) ≥ 8, +pT3a, +pT4, +PSA, + clinical stage (cStage) ≥ T3a + any of these preoperative findings (in pts with neoadjuvant AD): preoperative PSA ≥ 10 ng/ml, bx GS score > 7, + PSA ≥ 10 ng/ml + bx GS > 6. Pts had to have post RP PSA < 0.2 ng/ml, stratified by T, N, GS, and adjuvant radiation plan and randomized: Arm 1 (AD+ [cidence + gestatable for 2 ys] or Arm 2 AD + 6 cycles of m.12 ng/ml + P 5 mg 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 α = 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 1099-1107 when the DSMC recommended stopping accrual due to higher leukemia risk in Arm 2. 16% had N0 (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 (FU) 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 therapeutic strategy benefit cannot be extrapolated from different disease stages and the importance of adequate fix to the remarkable DFS and OS, irrespective of risk extent, may be result of risk def-

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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: Phoebe 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 patients.

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.

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 0 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 65%, respectively. Median TTNI was not reached yet. Of the 18 men with hormone refractory prostate cancer who had ADT deferred, 11/18 (66%) 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 SABR for OPC is feasible and well tolerated. The preliminary clinical outcomes in our series is limited by heterogeneity and size but data suggests that this approach is worthy of further prospective study.

Table: Patient and disease properties (n = 66).

<table>
<thead>
<tr>
<th>Factor</th>
<th>n (%)</th>
<th>Median (range)</th>
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<td>69-84</td>
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5022 Poster Session (Board #06), 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 randomized 2:1 to enzalutamide plus placebo or placebo alone. We used the training set to build a multivariable Cox model. Results: In the validation set, the AIC-based model predicted OS with a c-index of 0.69. The risk index was used to predict OS for patients treated with enzalutamide.

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 sa marium; we evaluated whether the timing of bone supportive therapy (BST) affected pain.

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 clinical characteristics. Results: 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 increase follow by return to baseline or lower. Results: Of 65 patients, 20 had baseline pain score > 0 and 34 were evaluable. Median Idoses 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 4/5 (80%) patients who did not receive BST. Pain flare occurred in 6/21 patients (29%) without BST and 2/13 (15%) with BST. Response/flare occurred in 6/21 (29%) patients who received BST within 1 month prior to first Ra223 dose.

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

**BCRA1/2**

**reversion mutations in prostate cancer identified from clinical tissue and liquid biopsy samples.** First Author: Suggahan Daniel, Foudation Medicine, Inc., Morrisville, NC

**Background:** Prostate tumors with genomic alterations (GA) in **BCRA1 or BCRA2** may be sensitive to treatment with PARP inhibitors (PARPi). However, secondary reversion mutations (revGA) can arise that may restore **BCRA** function and underlie reduced sensitivity to PARPi or platinum (PtPi) 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 1191 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:** 219111 (11.3% ± 1.4%) tumors had ≥ 1 deleterious **BCRA** GA. Of these, 7 samples harbored potential revGA in **BCRA1** (1) or **BCRA2** (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 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 TMMPS2 (fus), PTEN, CDKN2A were similar in revGA (0.5%) and non-revGA (0.4%) 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 **BCRA**-mutated tumors (0.9% vs 6.6%, p = 0.000002). Clinical histories for patients with reversion mutations will be presented. **Conclusions:** CGP of 1911 prostate carcinomas revealed ≥ 1 deleterious **BCRA1/2** 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 underlie resistance to PARPi or PtPi-based therapy. **BCRA** revGA can be detected from both tissue and liquid biopsies.

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, a week apart, castrate level (< 50 ng/dL) testosterone (T) and no ICD-9/10 code or therapy indicating metastasis. **Gleason grade (G)** groups relative to the Low risk group. These findings may further inform diagnostic and management strategies for combating disease progression.

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 hypothesized increased DNA damage by elaprepod (O) will complement anti-tumor activity of immune checkpoint blocking antibody, durvalumab (D), in mCRPC. **Methods:** Single-arm pilot study with accrual of 25 patients (pts) with mCRPC and biopsiase disease. Prior treatment with enzalutamide and/or abiraterone is required. **D** is given at 1500 mg iv q28 days × 0 300 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 (27/29), thrombocytopenia, lymphopenia, neutropenia, fatigue, UFT, 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.

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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: The Notch ligand Delta like gland 3 (DLL3) is a transmembrane cell surface protein aberrantly expressed in the majority of NEPC and a subset of castration-resistant prostate cancer (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 14/13 BEN (10%), 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, CAGA). 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 germline loss (85%), 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 further support investigation of Rova-T as a potential therapeutic agent for NEPC. A phase 1 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 (83.2%), nodal (56%) or visceral (8%) metastases, was collected. All received NAs as 2nd and 3rd line 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→NHA was 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.

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<td># pts</td>
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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 taken at baseline and at 4, 8, and 12 weeks. 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 µm) were seen in 29% of pts with clinical benefit compared to 60% in non-beneficiers. Analysis of monocyte polarization after initiation of therapy showed that reduction of M1 polarization was associated with improved 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 transcriptional 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 identify the safe, 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. Exclusions: 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 with an initial increase in exposure in the 80 mg dose level of 56% 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.

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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/m² q3w, 50%; 20 mg/m² q2w, 27%; 16 mg/m²q3w,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 treatment 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.

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<tr>
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<th>CABA</th>
<th>CABA rechallenge</th>
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<tr>
<td>Best clinical benefit*</td>
<td>51%</td>
<td>34%</td>
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<tr>
<td>Stable</td>
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<td>48.5%</td>
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<td>Progression</td>
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<td>PSA response</td>
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<td>Decrease &gt; 50%</td>
<td>71%</td>
<td>24%</td>
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<tr>
<td>Decrease ≥ 30%</td>
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<td>Median PFS (mo)</td>
<td>11.9 (11.59; 14.72)</td>
<td>7.8 (14.0; 10.12)</td>
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<td>Median OS (mo)</td>
<td>30.6 (24.28; 37.36)</td>
<td>13.4 (8.31; 15.08)</td>
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*Based on ECOG performance status, pain and analgesic consumption.

5035 Poster Session (Board #109), Mon, 1:15 PM-4:45 PM

Phase 2 biomarker-driven study of ipilimumab plus nivolumab (Ipilimumab) for AR-V7-positive metastatic castrate-resistant prostate cancer (mCRPC). First Author: Karim Boudadi, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: AR-V7+ mCRPC is an aggressive phenotype with a median PFS of 3-4 mo and OS of 7-9 mo. We hypothesized that AR-V7+ tumors would be enriched for DNA repair mutations, rendering them more responsive to combined immune checkpoint blockade. Methods: We enrolled 15 mCRPC pts with AR-V7+ CTCs (using a CLIA-certified assay) into a single arm phase 2 study. Pts received Nivo 3 mg/kg every 2 wk for 4 doses, plus Ip 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 response rate. Secondary endpoints: objective response rate (ORR) in pts with measurable disease, durable PFS (lack of progression ≥4 wk), PSA-PFS, radiographic (r) PFS, overall survival (OS), and frequency/intensity of AE’s. Results: 15 AR-V7+ men were enrolled, with median flt 8.4 (range 1.9–10.9) 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 AR-V7/AR ratio was 23% (range 3-75%), 6/15 men (40%) had pathogenic DNA repair gene mutations (BRCA2, ATM, MSH6, FANCM, FANC, POLH). Overall, the PSA response rate was 1/15 (7%), ORR was 2/15 (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). Grade 3-4 treatment-related AEs occurred in 7/15 (46%) men (including 2 hepatic abscesses, 1 colitis, 1 pneumonia); there were no treatment-related deaths. Conclusions: In this first study targeting AR-V7+ mCRPC, treatment with Ip/Nivo had acceptable safety and encouraging efficacy, particularly in men with DRD+ tumors. DNA repair mutations may be enriched in AR-V7+ prostate cancer, clinical trial information: NCT02601014.

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 chemotherapeutic-naive CRPC 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 achieved 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 CTA analysis. Seventy-seven percent of pts (27/35) had detectable CTCs; 11 of 35 pts (31%) had AR overexpression. Of the pts with N-terminal AR expression, 1/5 pts treated with AA and 5/8 pts treated with AA/CBZ had a PSA decline ≥50% from baseline. Conclusions: Real-time CTA 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.

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 trial of abiraterone acetate (ABI) plus prednisone (P) vs enzalutamide (ENZA) for metastatic castrate-resistant prostate cancer (mCRPC). First Author: Daniel Khalil, BC Cancer Agency, Vancouver, BC, Canada

Background: ABI + P and ENZA treatments are associated with side effects that may impact 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, cognitive and depression health questionnaires (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 level occurred in only 21% of the ENZA arm. 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.

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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 various cancers, to this point there is minimal evidence of activity in mCRPC. This is a report of avelumab, anti-PD-L1 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 11 ng/mL. 11 pts had Gleason score (GS) = 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 ≤ 2 treatment related adverse events (TRAES), fatigue being the most common. 4 pts experienced grade ≥ 3 TRAES including hyperglycemia (grade 3) and dehydration (grade 4).

Conclusions: Avelumab was administered as a 1-hour intravenous infusion every 2 weeks with restaging scans every 6 weeks. Five of 18 pts enrolled while on enzalutamide with a rising PSA doubling time (PSADT). 7 pts had stable disease (SD) prior to avelumab was compared with PSADT at 3 months (m) of treatment. Among 17 pts with available data, 3 pts had a prolonged PSADT which was defined as ≥ 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 1 pts had prolonged PSADT, 2 had a stable PSADT and 2 decreased PSADT at 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 patients with mCRPC. The analysis is under way to determine correlation with immune responses in the pts on this trial that had prolonged SD. Clinical trial information: NCT01772004.

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 99mTc-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 99mTc-EC0652 SPECT scan. The primary endpoint of Part B is median radiographic progression-free survival (pRFS). Other study evaluations are OS, PSA, and CT-based biomarkers. Results: Part A is now complete: the RP2 dose is 6.5 mg/m² on the basis of non-DLT transaminists. 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 were Gr1 and Gr2; grade 3 adverse events included hyperglycemia, fatigue, constipation and renal impairment. 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 2 patients (50%) has achieved an unconfirmed RECIST PR. Conclusions: The RP2 dose of EC1169 is 6.5 mg/m², EC1169 has been well tolerated in 20 pts at the RP2 dose. Imaging with 99mTc-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.
Clinical activity and safety of ASNO01, 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 Tauscig Cancer Institute, Cleveland, OH

Background: ASNO01 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. ASNO01 also exhibited 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 ASNO01 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, ASNO01 was well tolerated. Most drug-related adverse events were Gr 1/2 and included fatigue, constipation and nausea. At 400mg, 2 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 (Cmax, AUC and T1/2 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, ASNO01 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.

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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 Database from 1998 to 2001 who underwent RP within 12 months of CaP diagnosis were eligible. Biochemical recurrence (BCR) was defined as PSA > 0.2 ng/ml post-RP. Comorbidity conditions included coronary artery disease (CAD), cerebrovascular accident (CVA), type II diabetes (DB), hypertension (HT), elevated cholesterol levels (CHL), lung cancer (LC), cancer (CC), rheumatoid arthritis (RA), and diabetes (DB). Multivariable Cox proportional hazards (PH) analysis was used to examine comorbidity conditions (yes vs. no) and PSADT (< 3, 3-8.9, 9-14.9, and ≥ 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 were 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, AA vs. CA patients had greater CVD (10 vs. 6%, p = 0.0008) and OC (3 vs. 10%, 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 = 0.009) 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). Conclusion: Despite comparable health care access and distribution in clinical risk stratum and pathology features, race persisted in predicting poor CaP outcome. Disparity comorbidity for AA and CA men did not eliminate this difference. PSADT remained the most striking determinant of poor BCR-free survival.

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9.51; 95% CI, 1.11-81.52; P = 0.0398). CTC positive pts were less likely to
have an overall response (OR = 0.26; 95% CI, 0.06-1.08; P = 0.06) and increased expression levels of cell cycle proliferation (CCP) genes in non-
androgen treated 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 4.3 [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, HR for distant 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 allele that enhances dihydrotestosterone synthesis is associated with time-to-metastasis in men treated with ADT after RT for prostate cancer. Notably, 49% of men who 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.

5052 Poster Session (Board #126), Mon, 1:15 PM-4:45 PM
Association of CTC detection by AdnaTest with outcome on enzalutamide in chemotherapy-naive 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 clinical action of CTCs in patients with no CTCs detected by CellSearch (Samolka 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-naive CRPC patients 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 wks) was 23% (22/95). All CTC conversions had 0% decline in PSA 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 worse sPFS (median, 7.5 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 (median NRs, HR, 9.51; 95% CI, 1.11-8.52; P = 0.0398). CTC positive pts were less likely to have a ≥90% decline in PSA (OR, 2.38; 95% CI, 1.13-7.72; P = 0.02).

Conclusions: CTC detection using AdnaTest is associated with an adverse outcome in chemotherapy-naive 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 (AAP) primary resistance and cell cycle proliferation pathway activation with response duration in metastatic castrate resistant prostate cancer (mCRPC). First Author: Marsh Kohli, Mayo Clinic, Rochester, MN
Background: Genetic aberrations associated with resistance/response to AAP 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 in patients with a short or long response duration. 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/beta-catenin pathway genes, frequent deletion of negative regulators of Wnt pathway (DKK4, SFRP2, LRP6). Gene expression analyses revealed significantly reduced expression levels of Wnt/beta-catenin pathway inhibitors and increased expression levels of cell cycle proliferation (CCP) genes in non-responders. Median survival was 32 months for 82% decline in PSA; whereas only 22% (17/82) of pts progressed and switched treatments. Median TTTT was 10.1 months (IQR: 4.4-24.1). In multivariate analysis CCP scores of ≥50 predicted shorter TTTT (HR = 2.11, 95% CI: 1.17-3.80; p = 0.01). Conclusions: In metastases Wnt/beta-catenin pathway activation is associated with primary AAP resistance and increased CCP with acquired drug resistance. These findings offer molecular based predictive biomarkers in CRPC stage treatment. Clinical trial information: NCT01953640.
The immunomodulatory protein Dickkopf-1 (DKK1) defines a non-neuroendocrine subtype of metastatic castration-resistant prostate cancer (mCRPC) with low AR expression. DKK1 has been implicated as a suppressor of anti-tumor immunity and is a signature that can reproducibly predict outcome in CRPC and can improve on 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 (NCT02118812), 150 patients with biochemical recurrence were imaged. 63 patients were imaged using PET/CT (GE Discovery VCT) and 63 patients using PET/MRI (GE Sigma 3.0T PET/MRI). 110 patients received Laxis 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 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 ADT to therapy (15 patients, 12%), changing from ADT to radiation therapy (16 patients, 13%), and converting from radiation therapy to either active surveillance (16 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 converging a targeted systemic treatment or systemic treatment for the detection of occult metastases. Prospective studies are warranted to determine whether directed treatment towards PSMA-avid lesions affects long-term disease outcomes. Clinical trial information: NCT02918357.
SO58  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 Girdhar, Mayo Clinic, Rochester, MN
Background: The detection of full length AR (AR-FL) or AR variants (AR-Vs) in 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 CELLEXpress 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 observed. Blood based AR-FL or AR-Vs were detected in 50/53 patients with following distribution: AR-FL (41/53), ARV3 (9/53), ARV54 (8/53), AR12V (1/53), ARV14 (4/53), ARV7 (2/53), and ARV8 (2/53). Whole blood AR-FL transcripts were highly correlated to paired bone biopsy (r = 0.76). Elevated prostate specific antigen (PSA) status of either ARV12 or ARV45 was associated with worse OS (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 poorer 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.

SO59  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 Wodde, 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, SPGC-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-c2 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. Results: The median follow up was 10.4 years (range 5-16). The median age was 66 years. There were 104 deaths (13-120) and 120 (range 3-120) months for the HDR-BT/EBRT and EBRT groups respectively. KM plots revealed a 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. Conclusion: 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.

SO60  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.R847H) in blood samples. In 11 patients, plasma AR CN and mut were correlated with Enzalutamide (enza) and Abiraterone (abi) treatment outcomes. We first optimised multiplex ddPCR to accurately define AR CN and mut allelic frequency (Bland-Altman test: mean difference -0.02 95%CI -0.45 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), DFS (HR 2.18 95%CI 1.08-4.39 p = 0.03; HR 1.95 95%CI 1.17-3.31 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 mutation was observed in 8 (11%) postdoc but not pre-doc at-hired therapy and associated with a worse OS (HR 3.26 95%CI 1.47-7.01 p = 0.044). There was no interaction between AR and doc status (p = 0.83 for OS, p = 0.99 for DFS). Multivariate analysis, adjusting for AR CN and mut, previous doc, doubling 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 DFS (HR 1.96 95% CI 1.32-2.93 p < 0.001). Conclusions: Plasma AR status assessment using multiplex ddPCR identifies OS 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.

SO61  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 PCa (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. Conclusion: 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.

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3.52 (2.18, 5.69) p

Univariate OR (95% CI)

Number “lethal"

Author: Christopher Sweeney, Department of Medical Oncology, Dana-Farber Cancer Institute and Brigham and Women’s Hospital, Boston, MA

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Association of loss of tumor suppressor ZFP36 with lethal prostate cancer.

Univariate OR (95% CI)

Number “lethal”

Author: Christopher Sweeney, Department of Medical Oncology, Dana-Farber Cancer Institute and Brigham and Women’s Hospital, Boston, MA

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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 examines 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. < 30 kg/m²). 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 > 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 = 1.53, CI = 1.03-2.27, p = 0.028) but not for none vs. ≥ 6 (p = 0.44). MLR showed increased odds of GU for none vs. ≥ 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[Baseline vs. ≥ 6] = 2.27, CI = 1.54-3.33, p < 0.001; HR[1-5 vs. 1-6] = 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 (Habali JCO 2014), a (p-value = 0.013) levels were associated with OS. The HR for A was 0.99 (95% CI = odds of A for none vs. 1-5 = 0.99-0.99) and for D = 0.99 (p = 0.013) levels were associated with OS. The HR for A was 0.99 (95% CI = odds of A for none vs. 1-5 = 0.99-0.99). 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 relies 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 (<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 assess the time to 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: Prognosis 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.

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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 phosphodiesterase 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. Results: Patients with a high PDE4D7 score 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-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-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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Prior response to A or E does not predict sensitivity 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 CTC subtypes based on 15 pre-defined phenotypic CTC classifiers (Type A0). 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 outcome on E for all measures. Whereas similar outcomes were seen between K+ vs. 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: 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 clinical validation of the CTC subtype is planned.

5072 Poster Session (Board #146), Mon, 1:15 PM-4:45 PM
Identification of a CTC-based gene expression signature predictive 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 re-sponsiveness. Materials and Methods: 5ml of whole blood (-5ml) was obtained from 57 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. Sample size was considered sufficient to detect a 10% change in gene expression relative to the pre-treatment whole blood (p<0.05). Results: 94% (101/107) of pt samples. One, cell Type K, found in 25% (27/107) of pts, was associated with a statistically significant inferior outcome on E for all measures. Whereas similar outcomes were seen between K+ vs. 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: 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 clinical validation of the CTC subtype is planned.

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 pts who underwent radical prostatectomy for Gleason 3+3 PCa. We have developed a score to contact patients and offer them the possibility to use of precise PCR-based tools 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 2029. The volume of prostate was taken as a parameter. We computed the area under the ROC curve for each predictor (AUC). We then selected the best predictor combination using a forward stepwise approach from all predictors. The AUC threshold of 0.7. The new tool performed well in training and validation cohorts. Conclusions: PSA and radioclinical PFS and 0.89 for radioclinical PFS. In comparison, the AR-V7-only tool shows good predictive power for insignificant PCa in this population in poor predictive value when applied to an unscreened cohort of patients. Our novel tool performs well in training and validation cohorts. AUC threshold of 0.7. The new tool performed well in training and validation cohorts. The inherent selection bias due to analysis of a surgical cohort is acknowledged.

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5074 Poster Session (Board #148), Mon, 1:15 PM-4:45 PM

**Association of clinical recurrence (CR) and prostate cancer death (PCD) with a 17-gene genomic prostate score (GPS) value <20.**

**First Author:** Phillip G. Fieebo, 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 <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. Results: GPS was developed using Klein et al., standardized hazard ratios (std HR, HR for 1 SD change in the covariance) 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 2.58 [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 2.06,4.68], p <0.001, RM-corrected std HR 1.96, FDR <0.1%) after adjustment for baseline variables. Conclusions: GPS strongly predicts risk of CR and PCD in men with a very low risk of CR or PCD and should be considered for AS.

**Estimated 10-year RM-corrected risk of CR PCD.**

<table>
<thead>
<tr>
<th>AUA Risk Group</th>
<th>GPS Group</th>
<th>CR risk</th>
<th>PCD Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;20</td>
<td>1.8%</td>
<td>3.5%</td>
</tr>
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<td>&gt;20</td>
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<td>Intermediate</td>
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<tr>
<td>High</td>
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<td>1.0%</td>
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<tr>
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</table>

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 cutoff (proximal PSA, PP) that indicates the immediate occurrence 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 (11,296), 513 men with BCR (<0.2ng/ml) with PSADT <12 mos who received no adjuvant/salvage ADT/Rx were prospectively followed until radiological evidence of M+ are included in this analysis. All patients were evaluated yearly with PSA and scans at regular intervals until M+. Associations with MFS were compared using logrank test and Cox regression. Results: The PP is the most recent value >6 months prior to M+. Conclusions: PP was in 218 of 513 patients with BRPC (median follow up 9 years). Risk of M+ increased successively for PSADT 6.0-7.5, 7.6-8.5, 8.6-9.5, 9.6-10.5, 11-11.5, >11.5 at follow-up. PP >=10mg/ml significantly increased risk of M+ in pts vs PSADT <12 mos, regardless of PSADT subgroup, hazard ratio=2.95, p =0.0001. Median MFS was 4.0 years at PP >10mg/ml vs 20 years at PP <10mg/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 group in men with BRPC. PSADT subgroups >7.5 mos and PP >10mg/ml are independent predictors of MFS, adjusted for pt stage and Gleason score. PP >=10mg/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**

<table>
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<tr>
<td>MFS</td>
<td>(48 pts)</td>
<td>(21 pts)</td>
</tr>
<tr>
<td>P</td>
<td>Value*</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>49.44%</td>
<td>19.05%</td>
</tr>
<tr>
<td>5 years</td>
<td>47.38%</td>
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<td>7 years</td>
<td>47.87%</td>
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**PSADT 3.01-6.0 mos**

<table>
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<tbody>
<tr>
<td>MFS</td>
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<td>P</td>
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<td>5 years</td>
<td>61.38%</td>
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</tr>
<tr>
<td>7 years</td>
<td>49.87%</td>
<td>48.87%</td>
</tr>
</tbody>
</table>

*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 alapharin (Ra-223) as single agent or in combination with other therapeutics (Tx).**

**First Author:** Ryan Vance Dittamore, Epic Sciences, Inc., San Diego, CA

**Background:** Ra-223 prologises life in mCRPC pts with symptomatic osseous metastasis with inconsistent effects on PSA. Survival data in a large mCRPC cohort is limited 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 combination is lacking. We studied CTC counts and the prevalence 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 treatment 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 Ra-223 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 (median = 33% of CTCs). Which was no longer detected in 7/20 samples (median = 33% of CTCs). 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 analyses of these CTC subtypes are ongoing, and may help describe tumor evolution and sensitization to novel therapeutics.

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 cyclophosphamide/GVAX (Cy/GVAX) –Deg. Methods: Men with high-risk PCs (T1c–3b N0 M0, Gleason 7–10) were randomized 1:1 to Deg/GVAX240 mg SQ vs Cy/GVAX 2mg IV. Cells, 1 x 10^9 LNCA cell slurry 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/mm²). 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 vs. Deg. Results: Median MFS was 7.5 months and PP = 0.18 to show a 2-fold increase in mean CD8+ density with Cy/GVAX–Deg vs. Deg. Conclusions: Intratumoral immune infiltrates were marginally augmented by Cy/GVAX–Deg vs. Deg alone, while CD8+ and Treg densities were significantly greater in both arms (A+B) compared to group C (TABLE). CD8+ and Treg densities were marginally significantly correlated. 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 similarly consistent across groups. Clinical trial information: NCT01696877.
A secondary analysis of PSA response in RNR 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: RTGO 9902 was a randomized controlled trial of the addition of adjuvant chemotherapy (CT; paclitaxel, oral etoposide, and estramustine x 4 courses) 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 metastases (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 included: 190 without and 143 with CT. 37% of pts had a post-RT PSA < 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 ≤ 0.2 (HR 0.94, 0.56-1.58). Interaction p = 0.14. This trend was not observed for those with PSA > 0.2 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 0.63, 0.34-1.17) and not in the PSA≤0.2 group (HR 1.31, 0.65-2.63). OS did not show the same pattern (PSA > 0.2: HR 0.98, 0.55-1.77; PSA≤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) and biomarker guided regimens may be warranted.

Investigation of mechanisms of resistance to ipilimumab therapy with a pre-surgical trial in patients with prostate cancer. First Author: Jianjun Gao, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Anti-CTLA-4 therapy (ipilimumab) 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, oral etoposide, and estramustine x 4 cycles of adjuvant docetaxel (75 mg/m2 q21d + prednisone) in high risk, localized prostate cancer. Each patient received one injection of leuprolide (22.5 mg) on week 0 and androgen deprivation therapy (ADT), (leuprolide acetate, Tap Pharmaceuticals). Blocking of other immune checkpoints such as PD1/PD-L1 and/or VISTA may be important to enhance clinical benefit. Results: We observed a significant increase of immune cells including T cells and macrophages in post tumor tissues 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: We observed a significant increase of immune cells including T cells and macrophages in 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 subsets of CD68+ macrophages, without overlap with CD163, suggesting an M2 subtype. In vitro studies demonstrated that engagement of PD-L1 and/or VISTA pathways inhibited T cell responses. 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 PD-L1/PD-L1 and/or VISTA may be necessary to develop additional benefit for patients with prostate cancer. Clinical trial information: NCT01194271.
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% vs. 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 (+/- 1 standard error of the estimate) was 85.1 +/- 0.7% and 74.9 +/- 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.

Prostate cancer (PCa) in 696 hypogonadal men with and without long-term testosterone therapy (TTh): Results from a controlled registry study. First Author: Ahmed 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 (Gillis et al., Lancet Diabetes 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 = 350 ng/dL and 296 hypogonadal men (57-74) opted against TTh. Long-term TTh was initiated after 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 at months 3, 6, 9, 12, 18, 24, 36, 60, and 72 months 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 median 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 of 3, and a predominant Gleason score of 3. Tumor stage was T2a in 9 (100%), tumor stage T2b 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, T stage T2b in 2 (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.
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 HR gene, including BRCA1, BRCA2, or ATM as determined by local and/or central testing. All pts must have progressed on abiraterone or enzalutamide in the support investigating rucaparib as a treatment option in pts with mCRPC with benefit from rucaparib treatment. Pts (opment of a plasma-based companion diagnostic to identify pts who may benefit from rucaparib treatment. Pts will be enrolled in at least 100 sites worldwide. Clinical trial information: NCT02975934.

TPS5088  Poster Session (Board #161a), Mon, 1:15 PM–4:45 PM

A phase 1/1b mult-center, 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 objective is 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), 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 (n=400) will be enrolled at 224 sites worldwide. Clinical trial information: NCT02991911.

TPS5089  Poster Session (Board #161b), Mon, 1:15 PM–4:45 PM

Phase 1b/2 keynote-365 trial: Pembrozumab (pembrolizumab) 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, pembrolizumab monotherapy and pembrolizumab + enzalutamide demonstrated clinical activity in mCRPC pts with pathogenic variants in HR genes. Pembrolizumab monotherapy demonstrated clinical activity in mCRPC pts with pathogenic variants in HR genes. Pembrolizumab monotherapy demonstrated clinical activity in mCRPC pts with pathogenic variants in HR genes. Methods: Cohort allocation depends upon prior treatment: cohort A requires prior abiraterone or enzalutamide + docetaxel (cohort B), or enzalutamide (cohort C). Pembrolizumab (200 mg) will be administered every 3 weeks (Q3W) for 35 cycles or until PD. Pembrolizumab treatment will continue for up to 35 cycles or until PD or unacceptable adverse events (AEs). Patients in cohort B may receive an antibody-drug conjugate 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 objective is 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), 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 (n=400) will be enrolled at 224 sites worldwide. Clinical trial information: NCT02991911.

TPS5090  Poster Session (Board #162a), Mon, 1:15 PM–4:45 PM

A phase III trial comparing atezolizumab with enzalutamide 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 sequentialing of agents to optimize outcomes. Pts with mCRPC who progress on enzi have increased circulating PD-L1(PD-L1–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. Oncotarget. 2016). Atezolizumab therapy and 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 metastases, 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.

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TPS5039 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 sizeable 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 abiraterone acetate (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 (pDFS) will be assessed in Cohort A using RECIST 1.1 (soft tissue) and PCWG2 (bore) criteria. Key secondary efficacy endpoints include confirmed objective response rate, time to pain progression, overall survival (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, F87L), and have been found to have negligible blood-brain barrier penetration. In the phase 1 ARAFORT 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 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 endpoints include time to first SSE, time to first SSI, initiation of opioid use, pain progression, and worsening of physical symptoms, all measured at 12-week intervals. Safety will be assessed by adverse events. Trial is open to 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 177Lu-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, confirmative dose 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. 177Lu-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. abiraterone) and docetaxel (or unfit/refuse chemo) without limit of # prior therapies provided adequate organ function will undergo imaging with 177Lu-PSMA-HBED-CC PET/CT followed by escalating fractionated doses of 177Lu-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 expansions will occur at recommended phase 1 dose (RP2D) in a 2-stage design. The primary endpoint is determination of DL and RP2D. Secondary endpoints include toxicity, PSA decline rate, RECIST response, PFS, PFS2, OS. Correlatives include baseline/follow up PSMA imaging, whole body distribution of 177Lu-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-free survival (PSFS) 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 be studied to identify markers of response to 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 (40% at 6 months) or RP2D in a 2-stage design. Progression 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 18F-DCFPy 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 hormone cancer assay will inform personalized genetic marked 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, extraprostatal 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/m² 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.

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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 localised 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 39Fx or 46Gy in 23Fx 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) or abiraterone (AB) is 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 efficacy 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–2c, prostate-specific antigen [PSA] < 20, N0, M0, Gleason score ≤7 [3+4 pattern only]), Eastern Cooperative Oncology Group status ≤2 and estimated life expectancy > 5 years. Exclusion criteria include any prior PC intervention. Pts will be randomized to receive open-label oral ENZ 160mg/day once daily or AS 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 endpoint is time to PC progression (pathological or therapeutic). Secondary endpoints 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.
Clinical trial information: NCT00712218.

peritoneal lymph node metastases in 56% of the patients. Our data indicate progression-free survival despite detecting (and removing) sub-clinical retro-pelvic and para-aortic LNE in patients with AOC with both intra-abdominal within 60 days after surgery 3.1 vs 0.9% [p=0.049].

Furthermore, serious post-operative complications occurred in a higher median blood loss (650 vs 500 ml), and a higher transfusion rate in the LNE arm was 64 minutes longer (means: 352 vs 288 min), resulted was 26 months in both arms (HR 1.11, 95%CI 0.92-1.34 p=0.30). Surgery for treatment of HREC significantly improved 5-year FFS, with absolute and 3-year FFS for stage III was 75.4% for CTRT vs 63.4% for RT, p = 0.0292. Patients with stage III EC had lower 5-year FFS (69.6% vs 79.5%, p = 0.014). Three- and five-year FFS rates were 83.4%, 78.4% for TC, while the 5-year OS rates were 84.3%, 89.3%, and 88.4% respectively.

The superiority of chemotherapy regimens employing a taxane plus platinum agent regimens may be a reasonable alternative to AP. Clinical superiority of 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 after initial surgery and AP for endometrial cancer patients at high risk of recurrence after surgery. Methods: Patients receiving AP, DP, or TC as adjuvant chemotherapy for endometrial cancer were randomized to receive 6 cycles of doxorubicin (60 mg/m²) plus cisplatin (50 mg/m²) on day 1 (AP), docetaxel (70 mg/m²) plus cisplatin (60 mg/m²) on day 1 (DP) or paclitaxel (180 mg/m²) 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 OS (P=0.246) or PFS (P=0.087) 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 the 3 groups. Our data will definitely define the role of secondary cytoreductive surgery that should at least be considered as valuable option in pts with a positive AGO-Score. Clinical trial information: NCT01166737.

5500 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 2nd-line chemotherapy alone vs cytoreductive surgery followed by chemotherapy. 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 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 2nd-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<0.001). PFS-2 beyond 1st and 2nd relapse equaled or even exceeded PFS-1 before 1st 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-YRS was 83% instead of the protocol assumed 55-66%). 60% 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 definitely define the role of secondary cytoreductive surgery that should at least be considered as valuable option in pts with a positive AGO-Score. Clinical trial information: NCT01166737.
5504 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

An open-label, multicohort, phase II U维 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 wk (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

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<th>Best overall response (%)</th>
<th>Partial response (n = 7)</th>
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<th>Stable disease (n = 5)</th>
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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 (CT, experimental arm) reduces the rate of recurrence or death (ie., 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) of FIGO 2009 stage III 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 CT-R and 406-CT). Of those, 733 were eligible (344 CT-R and 360 CT), and 680 received the trial intervention (333 CT-R and 347 CT). Median follow-up is 47 months. Patients characteristics were balanced between arms. There were 201 (58%) > gr 3 toxicity events in the CT-R arm and 227 (63%) in the CT arm. The most common > gr 3 events were myelosuppression (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 CT-R vs. CT; CI 0.74 to 1.0. 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 0.28 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 exploratory analysis did not increase RFS in optimally debulked, stage III/IVA UC. Clinical trial information: NCT00942357.

5506 Oral Abstract Session, Fri, 2:00 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 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 (P) to cediranib given with chemotherapy and as maintenance (M). 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 (91.1, 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.

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 02-21; NCT01874353), maintenance olaparib (O) given after response to chemotherapy resulted in a significant improvement in PFS vs placebo (P) in patients with gBRCA-mutated (m) platinum-sensitive relapsed serous ovarian cancer (gBRCA-mutations) at 18 months (HR 0.7, 95% CI 0.59, 0.81). Maintenance olaparib compared with placebo differs in 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 -2.0, respectively, difference O minus P = -1.1; 95% CI: 0.5, 1.0, 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 < 0.0001) 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) (GEICO 1205/NOVA TRIAL). First Author: Yolanda Garcia Garcia, Hospital San Juan, Madrid, 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 iv. every 3w in experimental arm. The primary endpoint was complete macroscopic response (CMR) rate at IDS. Secondary objectives were safety, surgical feasibility, optimal surgical resection 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: The all groups had well balanced characteristics (Table). 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). Minor 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%, 0.566 - 1.984). There were no other 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 fistula, 1G3 entero-cutaneous fistula, 1G3 deep vein thrombosis, 1G2 bleeding, 1G1 surgical sepsis). Conclusions: NACT with Bevacizumab was feasible and improved the surgical outcomes at IDS in pts initially considered unresectable. Clinical trial information: 2012-003883-S1.

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. (HGSOCC). It is not known whether patterns of genomic rearrangement are predictive of clinical outcome in HGSOCC. Methods: This was a retrospective cohort analysis of whole genome sequences from 80 HGSOCC 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 ten kilobase to 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 (20.6% vs 9.1%, P=0.007). Multivariate analysis showed a hazard ratio for death of 2.1 associated with the Sig-High group (Table). Conclusion: A genomic rearrangement signature is associated with chemoresistance and poor prognosis in HGSOCC. Prediction of poor survival outcomes could allow early identification of women who may be candidates for clinical trials.

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 (ddCT) 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) is 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, Immunoreactive (I) type, Proliferative (P) type, Differentiated (D) type. We discovered the Mesenchymal transcriptome subtype might be sensitive to taxane chemotherapy. Therefore, we hypothesized that the MT type, which has the highest degree of mesenchymal transition, might be more responsive to ddCT than to TC. To test this, we performed a phase II study comparing the two treatments: ddTC (n=95) or TC (n=106). We categorized the patients into two groups based on the treatment they received: ddTC (n=95) or TC (n=106). Results: The all groups had well balanced characteristics, median age 60.0 y.o and 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). Minor 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%, 0.566 - 1.984). There were no other 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 fistula, 1G3 entero-cutaneous fistula, 1G3 deep vein thrombosis, 1G2 bleeding, 1G1 surgical sepsis). Conclusions: NACT with Bevacizumab was feasible and improved the surgical outcomes at IDS in pts initially considered unresectable. Clinical trial information: 2012-003883-S1.

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 into an Optimal Tumor Debulking (OTD) protocol. Germline and tumor BRCA1/2 mutation testing and methylation analysis were performed using a genome-wide methylation panel (Baym et al. 2019). We characterized two types of NACT pts: those with VS (Grade 1, G1) and those with DUPS (Grade 2, G2). 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 14.6 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 46.6 months, p = 0.0040). Of the 170 patients who received NACT, the ddTC group had significantly better OS 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.
Comprehensive genomic profiling (CGP) with loss of heterozygosity (LOH) to identify therapeutically relevant subsets of ovarian cancer (OC). First Author: Julia Andrea Elvin, Foundation 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. BRCAwt 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 215 genes. Tumor subtype counts were OC-S, n = 2770; OC-NS, n = 807; OC-NOS, n = 537 (mucinous, clear cell, endometrioid, neuroendocrine, carcinosarcomas, and low grade serous). Algorithms evaluated microsatellite instability (MSI), tumor mutation burden (TMB), TMB > 10 muts/Mb, and LOH (LOH-H = 14, LOH-L < 14). Results: 706/4114 (17.2%) OC had ≥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 (17.2% vs 5.8%, p < 0.005). BRCAwt 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 OC-LH-OC commonly had CCNE1 (19%), FAM137A (16.2%), ATP5A2 (7.4%), BRCA2 (3.3%), and MSH6 GA. Frequency of TMB > 2.5% and MS-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-NOS, including carcinosarcomas and mucinuous, are also LOH-H. Genes co-mutated in late stage LOH-H OC may be linked to treatment immunoresistance. CGP of this large OC cohort reveals molecular, rather than histologic, patient subsets that may benefit from PARPi. Reactive oxygen species (ROS) may mediate the immune response. Safety and updated efficacy data for 83 patients with PD-L1 advanced ovarian cancer. An updated analysis of the ovarian cancer cohort based on 15.5 months of follow-up is presented. Method: 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 in ≥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 ≥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 ≥1 prior therapies for recurrent/menopausal 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 confirmed partial response; 6 pts had stable disease (SD). The ORR was 9% (95% CI, 2.4%-30.2%). Tumor reduction was observed in 6/26 (23.1%); all 3 pts who responded completed 2 years of treatment. Median duration of response was not reached (range, 24.9-26.5 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). Conclusion: 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.

Pembrolizumab for previously treated advanced cervical squamous cell cancer: Preliminary results from the phase 2 KEYNOTE-158 study. First Author: J.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 the cervical cohort of this phase 2 study included patients (pts) 18 y or older with histologically confirmed advanced cervical squamous cell cancer, progression on or intolerance to ≥1 line of standard therapy, ECOG PS 0 or 1, and provision of a tumor sample for biomarker analysis. Patients received pembrolizumab 200 mg QSW for 2 y 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. Safety and updated efficacy data for 5515 metastatic 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 1xd 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 regimens as this might have a major influence on cost development in OC treatment.
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 ($2,426, P<0.0001). Supportive treatment costs were $4,320 for olaparib and $6,120 for rucaparib, revealing it ICER’s of month of life added to be $26,997 for bevacizumab, $17,757 for non-platinum, and $79,585 for platinum.

**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 IV low toxicities remains problematic and could widen disparities among those with limited access to care.

**References:**
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

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 Gynecological 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 recent CR, 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 gBRCA testing (gBRCAmut or non-gBRCAmut) and randomized 2:1 within each cohort to niraparib 300 mg or P until progressive disease (PD). Clinical trial information: NCT01874353. Results: Safety data from the randomized, controlled phase 3 NOVA trial showed niraparib and 30 (45%) niraparib and 23 (72%) P pts in the gBRCAmut and 65 (56%) niraparib and 45 (80%) P pts in the non-gBRCAmut cohorts had PFS events. PFS hazard ratios (95% CI) were 0.24 (0.131–0.441) in gBRCAmut and 0.35 (0.230–0.532) in non-gBRCAmut 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 gBRCAmut and 0.37 (0.236–0.567) in non-gBRCAmut cohorts.

**Conclusions:** Niraparib 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 #338), 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 neoadjuvant chemotherapy (NeoC) for recurrent 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/m2) to receive interval cytoreductive surgery alone (n=195) or interval cytoreductive surgery after HIPEC (n=196). HIPEC 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 5 month survival advantage. 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.
Randomized trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer. First Author: Myoung 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/m2, 90 min) or control arm (no HIPEC), intraoperatively based on residual tumor (size < 1 cm) 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 ≤ 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 was 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), neutopenia (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 3.0% in HIPEC and control group, respectively (p = 0.069). 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: NCT01914510.

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 47.2% in HIPEC and 27.4% in control group with TR0. For patients with NAC, 5 year survival for stages I, II, III, and IV were 76%, 69%, 50%, and 38% respectively. Pts with discordant TR had an even lower median PFS of 13.5 (SA and IA) and 12.9 (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 TR in pts with TR and pts with TR = 0. Pre-Chemo CT. The latter group showed PFS values in between those with surgically assessed post-op TR 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 these may lead to better definition of prognostic groups and the need for specific treatment strategies.

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Phase II study of cobanotinib (cabo) in patients (pts) with recurrent/metastatic endometrial cancer (EC): A study of the Princess Margaret, Chicago, and the Gynecologic cancer phase II consortia. First Author: Neesta C. Divatia. Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Recurrent/metastatic EC has a poor prognosis with no standard 2nd-line 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: PHL68 (NCI#9332) 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); 2/122). Cabo was well tolerated with common toxicities of fatigue, nausea, diarrhea & hand-foot syndrome. Most frequent Grade 3/4 toxicity was hypertension in 10% of pts. Fetal/liver perforations 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 months (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 months (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 25.2mths. Mutational analysis demonstrated presence of KRAS with PTEN or PIK3CA mutations in 10 (SEREND) pts, of whom 4 pts met the cabo enrollment criteria. The cabo cohort was endpt evaluable, but no T cell responses were observed in cabo vs placebo controls. The cabo data support further evaluation of cabo in EC. Clinical trial information: NCT01935934.

Phase I study of sequential ipilimumab in the definitive treatment of node positive cervical cancer: GOG 9992. First Author: Jyoti Maydev. 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 disease progression, pts were randomized to receive sequential ipi in dose levels 1: 3mg/kg, level 2: 10mg/kg, and an expansion cohort of 10mg/kg. Patients with rare histology EC were treated in a parallel exploratory cohort. Results: 12-wk PFS were observed; median PFS is 4.0 months (95% CI: 3.0 – 4.7) with estimated 6-mth PFS of 30% (95% CI: 15 to 46%). 3 pts had PFS >12 mths, 1 SER pt remains on study after 25.2mths. Mutational analysis demonstrated presence of KRAS with PTEN or PIK3CA mutations in 10 (SEREND) pts, of whom 4 pts met the cabo enrollment criteria. The cabo cohort was endpt evaluable, but no T cell responses were observed in cabo vs placebo controls. The cabo data support further evaluation of cabo in EC. Clinical trial information: NCT01935934.

A randomized phase III trial of cisplatin with or without S-1 in patients with FIGO IBV, 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 FIGO IBV cervical cancer patients. Patients with FIGO IBV, 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/m2 on day 1, followed by cisplatin on day 8, every 3 weeks) or cisplatin alone (50 mg/m2 on day 1, followed by cisplatin on day 8, 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. Major late toxicities were neutropenia (55% vs. 43%, 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. 21%, 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 IBV, 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 cervical cancer, we predicted all possible mutated neoepitopes 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 types markers, and HPV oncoprotein-associated genes. Normal tissue expression analyses were also performed using data from the GeneType-Tissue Expression project (n = 8,555). Results: We found that potentially immuno- genic 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 by load, and also 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 TGFβ1 expressions. Furthermore, ENO1 over-expression was observed in cervical cancer was associated with high HPV load, and ENO1 level also positively correlated with PD-L1 and TGFβ1 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 neoepitopes derived from mutations in known onco- genes. 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 oncolgic outcomes of radical trachelectomy in early-stage cervical cancer: A prospective multicentric cohort of 61 patients. First Author: Vincent Balay, 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 oncolgic 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 onco-logic 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 62.9 % 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 in-continence (4.9%), and one case of urethral fistula (1.6%). Nine patients had a major neurologic complication (4.7%). 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 2 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.

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 modality of 3D HDR-ICBT combined with complementary applicator-guided external beam radiotherapy (EBRT) was used for UCc patients 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 IB2-IVB) were treated with concurrent chemoradiotherapy. Aimed 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-CVT and IR-CTV was 70Gy (D90) and 50Gy (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 D2cc 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 D90 of bladder, rectum and sigmoid were 65.6Gy, 65.6Gy and 64.1 Gy, respectively and the 90.8%, 84.1% and 80.8%, respectively. Treatment was well tolerated. The grade 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 modality 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 ISBT.

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 a 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 between 1/1990-2016 were identified, with or without prior radiation. The treatment was approved. 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) (4500-5040Gy) and concurrent IV cisplatin (60mg/m2) on day 1 and etoposide (120mg/m2) 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 (1.5-not estimable) vs 2.9 months (0.9-4.6) for ES. Median OS (95%CI) was 31.8 months (1.9-56.0) for the whole cohort, 52.8 months (31.8-not estimable) for LS and 9.9 months (1.8-16.3) for ES. Conclusions: SCCC cohort treated with concurrent cisplatin/etoposide chemor/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.

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A randomized phase II evaluation of weekly gemcitabine plus pazopanib versus weekly gemcitabine 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 VEGFR-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/m² 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 vs paz) were: neutropenia (25% vs 15%) and fatigue (7% vs 1%), hypertension (11% vs 1%), elevated alanine aminotransferase (11% vs 0%), thrombocytopenia (9% vs 12%) and anemia (7% vs 2%). 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. The gem/ paz arm 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.

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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 combination-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 response. A total of 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 E1Spot. 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: 21.5, NE) vs 15.4 m (10.9, 19.3) for CP (p=0.0026). In the interim analysis of survival (OS), 4 deaths have been observed in CP+O vs 16 in CP (log rank p=0.00025). Cox proportional hazard analysis finds consistent results across centers, and no imbalance in identified risk factors explanatory for the emerging outcome of CP+O vs CP. Conclusions: This study suggests simultaneous day vaccination with O on alternate cycles of front line CP leverages 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 #358), 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 the 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 with 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 unselectable FIGO stage IIIC/IV ovarian, tubal or peritoneal adenocarcinoma (EJC 2017;70:13-32). 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 neoadjuvant CP or B (15 mg/kg), IDS for eligible patents, then 1 c of CP + 3 c of CP + B of. 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: 97 pts (49 CP vs B) were randomized (n=37 CP vs B). Complete response (CR) or partial response (PR) at c2 were 46% (95% CI: 35-59) vs 64% (95% CI: 54-72). CR was observed in CP+3 c of CP+3 c of CR (10% CP vs 20% B), proteinuria (10% CP vs 0% B), deep vein thrombosis (5% CP vs 4% B), neuropathy (5% CP vs 1% B), and grade 3-4 toxicity was observed in 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: 21.5, NE) vs 15.4 m (10.9, 19.3) for CP (p=0.0026). In the interim analysis of survival (OS), 4 deaths have been observed in CP+O vs 16 in CP (log rank p=0.00025). Cox proportional hazard analysis finds consistent results across centers, and no imbalance in identified risk factors explanatory for the emerging outcome of CP+O vs CP. Conclusions: This study suggests simultaneous day vaccination with O on alternate cycles of front line CP leverages 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.

5539 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 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 may fall 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.

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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 with 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 resistant OC.

**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 2^nd^line. Pts received up to 6 cycles. The primary 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 declare ORR > 30% (α = 0.055).

**Results:** 33 pts were enrolled (30 pts evaluated). Median age was 57 years (range 32-80). 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 PSA 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 neuropenia – 67.7%, nausea – 61.3%, weakness – 29%, thrombocytopenia – 22.6%, neuroapathy – 19.4%, vomiting – 19.4%.

**Conclusions:** Quisinostin in combination with paclitaxel and carboplatin in pts with recurrent platinum resistant ovarian cancer showed high efficacy and good tolerability. Clinical trial information: NCT02948075.

**NHB of platinum-sensitive treatment options in the era of biologics:**

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<tr>
<th>Regressor</th>
<th>ASCO NHB</th>
<th>Patient-weighted NHB</th>
<th>P value</th>
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<tbody>
<tr>
<td>Platinum-based chemotherapy + taxane (ICON4)</td>
<td>35</td>
<td>27</td>
<td>0.009</td>
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<td>Carboplatin dosometric (GINPLO)</td>
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<td>Platinum-based chemotherapy + bevacizumab (OASAN)</td>
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<td>Maintenance paclitaxel (Study 13)</td>
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<td>Maintenance mirabepa (NONA)</td>
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NHB = Net Health Benefit (based on PFS); BRCA = germline BRCA alterations; ABRCA = at wild-type germline BRCA; HRD = homologous recombination deficiency

**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 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 (CAIRO2) = 31 pts were enrolled (30 pts evaluated). Median age was 57 years (range 32-80). 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 PSA 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 neuropenia – 67.7%, nausea – 61.3%, weakness – 29%, thrombocytopenia – 22.6%, neuroapathy – 19.4%, vomiting – 19.4%.

**Conclusions:** Quisinostin in combination with paclitaxel and carboplatin in pts with recurrent platinum resistant ovarian cancer showed high efficacy and good tolerability. Clinical trial information: NCT02948075.

**NHB of platinum-sensitive treatment options in the era of biologics:**

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NHB = Net Health Benefit (based on PFS); BRCA = germline BRCA alterations; ABRCA = at wild-type germline BRCA; HRD = homologous recombination deficiency
A high number of ovarian cancer cases display a promoter hypermethylation and low-grade profile (sensitivity: 0.93). 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 carriers 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 -like classifier identified both BRCA1 and BRCA2 mutation status (n = 7) with a sensitivity of 0.93 (46/49). The complementary use of both classifiers led to the detection of 22 of 25 somatic mutations in BRCA1 (16/16) or -like or -like classifier identified both BRCA1 and BRCA2 mutation status (n = 7) with a sensitivity of 0.93 (46/49).

**Background:**
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. **Results:** A BRCA1-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 -like classifier identified both BRCA1 and BRCA2 mutation status (n = 7) with a sensitivity of 0.93 (46/49). The complementary use of both classifiers led to the detection of 22 of 25 somatic mutations in BRCA1 (16/16) or -like or -like classifier identified both BRCA1 and BRCA2 mutation status (n = 7) with a sensitivity of 0.93 (46/49).

**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 BRCA1-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.
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 Takeko, Department of Obstetrics and Gynecology, National Defense Medical College Hospital, Tokorozawa, Japan

Background: Erubulin 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 erubulin and oxaliplatin (ErOX) 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-ErOX consisting of B (2mg/kg), erubulin (1mg/m²) and oxaliplatin (30mg/m²), three weeks on and on week off, 4weeks. 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 (≥ 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 36% and 97%, respectively. Median progression-free survival was 4 months (range: 1–27+). Adverse events of AE with grade 3/4 were observed in 4 patients (11%). Non-hematological AE greater than grade 2 was observed in one case: hypoalbuminemia and edema, which were manageable and tolerable. As there were 10 responders (≥ 2), 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 ErOX administration was considered for additional investigation for patients with PR-ROC. Serum mutated p53 and/or IL-6 could be biomarkers in PR-ROC patients treated with weekly B and ErOX.

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 (db) 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 db Sx in the management of advanced OvCa. Methods: Only Stage III and IV Pts in National Cancer Database (NCDB) from 2006-2014, that underwent db surgery 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 test was used for the analysis. The survival in the three groups was as follows. 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 C 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. This may be secondary to less bulky 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 db 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.

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 soravantin (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 soravantin (IMGN853), in combination with bevacizumab (BEV), carboplatin, PLD, or pembrolizumab in adults with FRα-positive EOC, primary peritoneal, or fallopian tube tumors (NCT02606305). This is 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 each cycle (PLD; BEV or carboplatin). The study is ongoing. Results: A total of 34 patients were enrolled in the first 3 cohorts. IMGN853 was escalated from 5 to 6 mg/kg. Carboplatin and PLD dosing were escalated from AUC5 and 30 to 40 mg/m², respectively. BEV dosing remained constant at 15 mg/kg. Diarrhea, nausea, and fatigue were common across cohorts (all grades; 33-57%) and mostly grade (i.e. ≤ 2), consistent with the IMGN853 safety profile from the earlier phase I monotherapy study. AE of interest related to the combination trials was hematologic. More frequent were grade 1-2 anemia, platelets and neutrophil (36%) and grade 3-4 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 (≤ 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 anticipated based on the 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Two prognostic populations of ovarian cancer patients defined by CA125 kinetic 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 was 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 re-producible 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 AGO 7 & (HR=6.0 to 8.3) and ICON 7 poor proggn groups (PFS HR=2.24 PFS, OS HR=2.21; 9.2-6.1). KELIM prognostic value was independent on regimen arms (Table), maintained within ICON7 proggn groups (best OS gain with bevac if poor proggn & unfav KELIM), and better than GCIG CA125 (inconsistent proggn 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.

**Table 1:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Favorable KELIM (n=278)</th>
<th>Unfavorable KELIM (n=176)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<tr>
<td>AGO OVAR 9 CP</td>
<td>25.6</td>
<td>11.6</td>
<td>0.01</td>
<td>36.3</td>
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<tr>
<td>AGO OVAR 9 CP + Gemcitabine</td>
<td>23.3</td>
<td>13.9</td>
<td>NS</td>
<td>46.7</td>
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<tr>
<td>AGO OVAR 7 CP</td>
<td>25.2</td>
<td>11.3</td>
<td>NS</td>
<td>46.2</td>
</tr>
<tr>
<td>AGO OVAR 7 CP + Topotecan</td>
<td>25.2</td>
<td>2.8</td>
<td>NS</td>
<td>46.2</td>
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<tr>
<td>ICON 7 CP</td>
<td>20.7</td>
<td>13.4</td>
<td>NS</td>
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</table>

*NS: not reached*
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 PROFVE-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/m² or Carboplatin AUC5/PLD 40 mg/m² 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 0.65-1.04) for the experimental vs. standard arm, and 11.6 months vs 8.5-13.1 months) for the experimental vs. standard arm, 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 (BRCAm) 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 BRCAm 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 BRCAm 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 BRCAm testing. Primary endpoints were BRCAm testing TAT (time from initial counselling to the provision of test results or post-BRCAm testing counselling [whichever occurred latest]); pts satisfaction with the oncogenetic testing model, evaluated using pre- and post-BRCAm testing surveys; and clinicians’ opinion on the value of this new testing pathway, evaluated using a post-BRCAm testing survey. Results: For the 700 evaluable pts enrolled (US = 317; EU = 383), pre-BRCAm 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 maintained due to the time frame of 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 = highest satisfaction). 93.6% of pts were happy to have received genetic testing as part of an existing oncologist appointment, and more than 90% 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 BRCAm 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 BRCAm 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 successfull 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’Hebron 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 pts who were randomized to PARPi in the controlled, double-blind phase 3 ENGOT-OV16/NOVA trial. To more fully characterize the NOVA trial patient population, we analyzed survival and 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 eval-

engaged. Clinical trial information: NCT01388621.

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. We have recently reported a 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 HGS-OvCa patients were stratified into two subtypes within TGCA cohort (p < 0.001). In both cohorts, increased IC0G (n = 92) was 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 IC0G cohorts we remarkably correlated (Pearson r = 0.94, p < 0.001), relative to the correlation between HR and standard risk subtypes within TGCA cohort (r² = 0.18). We then identified molecularly matched cell line models for in vitro study, finding that HR cell lines (Kuramochi, OVvate, OAW26, 59M) were significantly more resistant to cisplatin relative standard risk cell lines (COV318, TYK-NU, OVCAR4), (IC50 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 sensitivity to paclitaxel. A genome-wide knockout screen using CRISPR-Cas9 has identified several candidate genes mediating this observed platinum sensitivity to paclitaxel. A genome-wide knockout screen using CRISPR-Cas9 has identified several candidate genes mediating this observed platinum sensitivity to paclitaxel.

Conclusions: NBS can be used to identify a molecularly distinct subtype of HGSO characterized by poor patient survival and primary platinum resistance.
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 Mi6-1 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 45.6 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, underlining the heterogeneous character of this disease.

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 differen-
tiated serous and adenosarcoma) were compared to all other tumor (OT) types (low grade serous and endometroid, 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 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 ID and Stage I/II compared to OT tumors. Survival for Type 2 tumors was similar regardless of method of diagnosis.

<table>
<thead>
<tr>
<th>Ovarian tumor type by diagnosis method.</th>
<th>Type 2</th>
<th>OT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>144 (48)</td>
<td>41 (138)</td>
<td>0.07</td>
</tr>
<tr>
<td>- Never screened</td>
<td>15 (51)</td>
<td>67 (162)</td>
<td></td>
</tr>
<tr>
<td>- Post-screening</td>
<td>70 (44.9)</td>
<td>17 (25.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>- Internal</td>
<td>25 (16.0)</td>
<td>6 (9.0)</td>
<td></td>
</tr>
<tr>
<td>- Screen Detected</td>
<td>46 (29.5)</td>
<td>36 (53.7)</td>
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</tr>
</tbody>
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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 for treatment 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 pelvic, 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 89 (mean=52; SD: 18.33). 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 pelvic 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 recurring 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 Vigen 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 established. 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 (OEGG), 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 (MO), 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 OEGG, 14 BENIGNG and 7 HEALTHG). 68% were high grade serous subtype; mostly 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 OEGG. 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 MO and M4 (p = 0.02). No differences were seen in the other determinations. cfDNA-ALU115 was 1.40178 ng/ml (95% CI 1.8066-2.990) in the OEGG, 0.6983 (95% CI 0.44832-0.87935) in BENIGNG and 0.59923 in HEALTHG (95% CI, 0.14449-1.05397). The difference was significant between OEGG and BENIGNG (p = 0.017) and near the significance between OEGG and HEALTHG (p = 0.001). cfDNA integrity was calculated by ALU247/ALU115, and after interval surgery (M4). This study was approved on May 2013 by the corresponding Central Research Independent Ethics Committee.

Conclusions: cfDNA and CTC are new biomarkers that might have an important role in the diagnosis and monitoring of OEC.

5567 Poster Session (Board #390), 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 II/III clinical trials were included. Selection (mut) allele fractions (MAFs) were corrected for tumor purity and defined as clonal (cl) (> 40%) or subclonal (scl) (< 40%); PAMi: PI3K/AKT/mTOR phosphorylation; clonal benefit rate (CBR) = complete/partial response or stable disease > 4 months (m); and (ii) ratio TTP on PAMi/ TTP on non-standard chemotherapy (C). Results: From 2010 to 2016, 264 GYN pts (152 ovarian(OC); 75 endometrial(EC); 37 cervical(Cc)) were included; 50 pts received PI3K inhibitors (PI3Ki) and 77 pts received PI3K and PTEN inhibition (PI3K/PTEN); 23 pts had ovarian cancer (OC) and 25 pts had endometrial cancer (EC). Of 405 clonal (cl) mutations, 24% were PIK3CA (PIK3CA mut); 19% were PTEN (PTEN mut), and 11% were KRAS (KRAS mut). Clonal mut (cl) were more frequent in OC (p = 0.03). We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi. We found that the number of prior lines was 2 (1-6) and 34 pts (68%) received neoadjuvant chemotherapy (neoChemo). Of 4 KRAS mut pts, none had CBR with single agent PAMi.
Surgery, improves survival outcomes, and helps pave the way for fertility-saving surgery. Early cyto-reductive surgery offers a chance for cure in patients with advanced ovarian cancer. Of the 17 patients who were both 94.4% and 94.4%, fertility-saving surgery was carried out in all the 17 patients. A median follow-up of 83.5 months, 17 patients were free of recurrence. 5-year DFS and OS rates were both 94.4%. Fertility-saving surgery was carried out in all the 17 patients who were retrospectively reviewed. Results: One or 2 cycles of BEP regimens were prescribed to the majority of patients preoperatively. At the completion of NACT, the all 18 patients had ECOG ps ≤ 1. Seventeen of them (94.4%) exhibited clinical partial tumor regression and (15.6%) 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 then undergone to follow-up after macroscopic disease, of 16 patients 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 rates were both 94.4%. Fertility-saving 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 thorough and safer cyto-reductive surgery, improves survival outcomes, and helps pave the way for fertility-saving surgery.

A phase 1 dose-escalation study of intraperitoneal (IP) cisplatin, IV/IP paclitaxel, IV bevacizumab, and oral olaparib for newly diagnosed adnexal 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/m² IV on 3 hours on Day 1, Bev 15 mg/kg IV on Day 1 (starting cycle 2), Cis 75 mg/m² IP on Day 2, Tax 60 mg/m² IP on Day 6. Bev is continued every 3 weeks for 21 treatments after chemotherapy is completed. In addition, Ola is given at escalating doses (50/100/200 mg tabs BID) on Days 2-8 during cycles 1-6, and then 300 mg 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%), fatigue (18.8%), 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 200 mg BID, while maintenance Bev + Ola dose at 500 mg BID continues appears feasible for lowing IV/IP. Updated results will be presented. Clinical trial information: NCT02121990.

Phase I study to evaluate the tolerability, pharmacokinetics (PK) and pharmacodynamic (PD) of PM01183 (Lubrinitcend) in combination with olaparib in patients with advanced solid tumors. First Author: Andres Poveda, Clinical Area of Gynecologic Oncology, Instituto Valenciano de Oncologia (IVO), Valencia, Spain

Background: PM01183 (Lubrinitcend) 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 E et al. ASCO 2014.abstr #5505). Olaparib (AZD2281, KU-0004360) is a 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 PM01183 in combination with short course of Olaparib tablet formulation (days (d) 1-5) of 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-h2AX) profiles at 0h, 4h, 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 + Olaparib 250 mg BID) on Day 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 combined with IP Cis, IP/IP Tax using a 3+3 dose escalation scheme. 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 + Olaparib 250 mg BID) on Day 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 combined with IP Cis, IP/IP Tax using a 3+3 dose escalation scheme. 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 + Olaparib 250 mg BID) on Day 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 combined with IP Cis, IP/IP Tax using a 3+3 dose escalation scheme. 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 + Olaparib 250 mg BID) on Day 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 combined with IP Cis, IP/IP Tax using a 3+3 dose escalation scheme.

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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 with secondary malignancies such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) caused by use of certain chemotherapeutic agents that interfere with DNA. This study assessed the 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 0.35 (0.1%) in OC-BRCA pts, 0.60 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.

**Conclusions:**

- The study identified 23,862 OC pts and 281,473 BC pts with exposure to DNA damaging therapy.
- The incidence of MDS and AML was higher in OC and BC pts.
- BRCA testing was associated with a lower incidence of secondary MDS and AML.

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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 patients were grouped according to the duration of medication, patients with longer duration of medication (≥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 benefits among these settings with no 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.

Racial disparities in ovarian cancer survival in New York state. First Author: Sarah Madhu Tanikin, 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 among 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) chemotherapy following surgery benefited blacks with 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 in white in New York State. Understanding modifiable factors on racial disparities is imperative to reducing racial based differences in outcomes.

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 immunochemistry (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 treated with Pembro. Genomic analysis of baseline tumor tissue was available for 3 pts with PD-L1 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 + SD]). Nine pts were platinum-resistant, 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 hypotension. Preliminary correlative data showed no significant change in CD4, CD8 and myeloid-derived suppressor cells in peripheral blood after Pembro treatment. Mean PD-L1 expression on CD4 and CD8 T cells on baseline tumor tissue (measured as product of PD-L1+ cells and the per cell expression of PD-L1 [% of mean fluorescence intensity]) was 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 BRAF mutations. Conclusions: In HGSOC, pts with higher PD-L1 level on tumor CD4 and CD8 T cells and higher mutation burden at baseline may have 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 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 TTFFields. 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 drug. Most patients were reported to have moderate to 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 125 response, translating into a decrease of 50% or more in serum levels. The median OS was not reached. Conclusions: TTFFields concomitant to weekly paclitaxel is feasible and safe in ovarian cancer patients. This data support further clinical testing of TTFFields with chemotherapy in ovarian cancer. Clinical trial information: NCT02244502.
Background: The prediction of tumor chemoresponsiveness and treatment toxicity is crucial for optimal patient care in high-grade serous ovarian cancer (HGSOC). 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 HGSOC. Methods: Tumor tissue, and serial plasma samples at diagnosis and during primary therapy were obtained from five patients with FIGO Stage IIIc HGSOC. 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 HGSOC. Further, the ctDNA gene panel annotations showed concordance with the chemoresponsiveness and treatment toxicity profiles, suggesting that ctDNA gene panel may be a feasible approach to individualize treatment of HGSOC patients.

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), Hispanic (NH), Asian (NAA), Black (NAB), and Other (NAO). The primary outcome measure was OS. Cox proportional hazards model was used to compare OS by race/ethnicity. Pt and clinical factors, including age, income, BRCA status, BMI, ASA, grade, carcinomaatosis, 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 NH (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 a 1cm residual (OR 2.32, 95%CI 1.1-4.9, p=.03). Median OS was 13.0, 1.6 and 13.0 months for NHW, NHB and A, 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 HGSOC. Further, the ctDNA gene panel annotations showed concordance with the chemoresponsiveness- and treatment toxicity profiles, suggesting that ctDNA gene panel may be a feasible approach to individualize treatment of HGSOC patients.

5585 Poster Session (Board #407), 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: Qiao Yu 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-cannibalistic 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-characterized 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 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.
Activity of lurbabin (PM01183) as single agent and in combination with other agents in patients with endometrial cancer. First Author: Martin David Forster, University College London Hospitals, London, United Kingdom

Background: Lurbabin (L) is a new anticancer drug that blocks trans-activated transcription, induces DNA double-strand breaks and modulates the tumor microenvironment. Advanced endometrial cancer (EC) is an urgent medical need. Methods: Activity in EC patients was reviewed in 3 trials: a phase I study of lurbabin 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. Lurbabin was the most frequent histology. Median (range) of prior chemotherapies for advanced diseases was: L=DOX, 10(2); L=TAX, 2(1-3); L, 10(2). Responses were observed in the 3 studies (see table). Main adverse event was myelosuppression (grade 3-4 neutropenia/thrombocytopenia). 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: Lurbabin is active as single agent and in combination with patients 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: NCT01970516

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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, Montreal, 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 2nd-line 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 (NC199323/NCT01959394) 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 1st-line 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 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 (55%). Median PFS was 3 mt (95% CI 2.7 – 4.6) with estimated 6-mt PFS 13% (2 to 33%). Toxicity was manageable. Most frequent events were fatigue and GI upset. Most frequent > Grade 3 toxicities were hypertension (5), anemia (4), diarrhea (2). Four pts had GI fistula (2) or perforation (2). Mutation profiling in archival tissue showed TPS3 (73%), PIK3CA (40%), KRAS (27%), PTK7 (27%), PTPN13% with >1 mutation (present in 4 of 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 trials are required to define depth and durability of response and identify relevant biomarkers. Clinical trial information: NCT01959394.

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 6/2012 to 12/2016 who had MGPT at our institution. Demographics, family history, genetic testing results, and tumor characteristics were collected and analyzed using χ2 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 (30%) of patients with a 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, MUTHY, CHEK2). 1 (0.8%) had both MSH2 and CHEK2 mutation. Three patients had previous testing and were found to have a BRCA1/2 mutation and the other was on Tamsoxifen 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 MUTHY with MGPT. These accounted for 29% of the mutations and would have not been 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.

Role of adjuvant chemotherapy 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 chemotherapy (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. Methods: We studied 2000-2011 women with advanced high-grade endometrial cancer treated in a large population-based database. Results: Of 2,735 eligible women, 13.1% received CRT vs. 42.5% CT alone vs. 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-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 CRT (HR 1.34; 95% CI 1.09-1.64) had better 5-year OS compared to CRT. In a subgroup analysis for breast cancer patients, chemotherapy (CT) vs. no chemotherapy (CT) vs. CRT was more pronounced for endometrioid histology and women <75 years of age and was more pronounced for endometroid (HR 1.72; 95% CI 1.22-2.41) vs. non-endometroid 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 CRT 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.
On the page, the text is about a study comparing the interval time between surgery and adjuvant therapy in patients with early stage endometrial cancer. It discusses the methods, findings, and conclusions of the study, including the association between delayed adjuvant therapy and overall survival. The text also mentions the role of insurance status, race, and other demographic factors in delayed treatments. Additionally, there is a discussion on the use of adjuvant therapy and its impact on survival rates.

The text also includes a mention of a Phase I trial that included 28 evaluable patients treated with ONC201, a specific antagonist of the G protein-coupled receptor DRD2, to evaluate its antitumor activity. The trial included patients with advanced endometrial cancer with prior surgery and radiation.

A table provides information on the number of somatic SNVs in different types of tumors, showing variations across different subtypes. The table also includes information on the number of pathogenic SNVs, disease progression, and other relevant clinical endpoints.

Overall, the text provides a detailed overview of the study's methodology, results, and implications, focusing on the role of adjuvant therapy and genetic variations in determining outcomes for patients with early stage endometrial cancer.
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=0.01), 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/TILs (97%); LMR-low/TILs+ (91%); LMR-low/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. 

<table>
<thead>
<tr>
<th>OS VARIABLE</th>
<th>HR (95% CI)</th>
<th>P VALUE</th>
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<tbody>
<tr>
<td>LMR low vs. high</td>
<td>6.4 (1.3-30.6)</td>
<td>&lt;0.01</td>
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<tr>
<td>Stage III vs. II</td>
<td>4.8 (1.5-16.8)</td>
<td>&lt;0.01</td>
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<tr>
<td>Endometroid G3, serous vs. Endometroid G1-2</td>
<td>9.9 (2.4-32.1)</td>
<td>&lt;0.01</td>
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<tr>
<td>DFS Stage III vs. I-II</td>
<td>8.3 (2.3-29.6)</td>
<td>&lt;0.01</td>
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<tr>
<td>Endometroid G3, serous vs. Endometroid G1-2</td>
<td>10.4 (2.4-50.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TILs present vs. absent</td>
<td>0.1 (0.03-0.5)</td>
<td>&lt;0.01</td>
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5595 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 included tumor characteristics, prior therapy and trial therapy and outcome. Results: 38 pts, median age 59 years (21-74) with EC (19) or CVC (19) were identified. Median prior therapies included 1 prior anticancer therapy. 1 pt had 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 sequencing (NGS) using a targeted panel with actionable mutations identified. Specific subtypes were reviewed. Data comprised pt and tumor characteristics, prior therapy, and EC and CVC pts treated in a phase 1 unit. Early phase trials may be a suitable option for pts with good performance status and safety. Conclusion: 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.

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 in time. However, this process 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) differentiated endometrial cancer patients with 100% accuracy in blood plasma and 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.
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 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 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.
Pts with OC associated with a deleterious (PARP) inhibitor rucaparib is approved in the United States for treatment of overall survival, and pt-reported outcomes. Safety will be summarized de-

randomized 2:1 to receive rucaparib (600 mg BID) (n = 230) or chemo-

negative BCRA1 to assess the benefit-risk profile of PARP inhibitors vs current SOC as been evaluated in the maintenance setting. Randomized studies are needed to assess the benefit-risk profile of PPAR inhibitors vs current SOC as treatment for BCRA1- or BCRA2-mutated, relapsed, high-grade OC. Methods: ARIEL4 (NCT02859544) is evaluating rucaparib vs chemotherapy as treatment for pts with germline or somatic BCRA1- or BCRA2-mu-
tated, relapsed, high-grade OC (regardless of histology) who have recurred on chemotherapy regimens. Approximately 345 pts will be randomized to 2:1 to receive rucaparib (600 mg BID) (n = 230) or chemo-
therapy (n = 115) and stratified by progression-free interval after their most recent platinum regimen. Pts with platinum-resistant (progressive disease [PD] > 6 mo after last platinum) or partial 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 che-

clinical trial information: NCT02859544.

TPS5605
Poster Session (Board #424a), 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 BCRA-mutated high grade serous ovarian cancer (HGSOC). Bev-

acizumab is an anti-VEGF monoclonal antibody indicated in the EU in first line chemotherapy for the treatment of OC in combination with cytotoxic therapeutical 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 placebo-controlled, Phase 3 study to evaluate 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: PFS according to RECIST 1.1 Secondary objectives: PFS2, OS, Safety, PRO/QLQ, TFS, TSST. All pts will undergo tumor BRCA testing prior to randomization. Central (BRCA testing [tumor]) will be performed in combination with specific cytotoxic therapeutical agents. 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 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 BCRA mutations (BRCAm) and advanced ovarian cancer (OC). BRCA mutations are genetic alterations leading to homologous recombination deficiency (HRD) and tumour susceptibility to DNA-damaging agents, including platinum-based chemotherapy. 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 of olaparib in pts with platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer. Eligible pts must have HRD status determined by genetic test results: germline BRCAm; MyChoice HRD-positive and wildtype herd Southern Europe and we excluded patients with co-mor
cinate CYP3A4 inhibitors or inducers; and symptomatic uncontrolled brain metastases. Pts 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. All pts will receive olaparib (15 mg/kg every three weeks) for 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 0.5 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.

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TPS5609 Poster Session (Board #426b), Sat, 1:15 PM-4:45 PM


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), an investigational agent targeting the 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 at poster discussion ESPMO 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 RECIST 1.1 and GCIG CA125. 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 0.01 5-sided level of statistical significance (or equivalently with 80% power at the 0.10 level of statistical significance), using a 3-outcome design. Secondary endpoints include objective response rate (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 and 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 (ORUK141442/52). Clinical trial information: ISRCTN16426935.

TPS5610 Poster Session (Board #427a), Sat, 1:15 PM-4:45 PM

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 Weill 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 been in the metastatic setting. Vizutusertib (AZD2014) is a dual mTOR inhibitor that has shown promising preliminary activity in high grade serous ovarian cancer (HGS) patients in a phase I trial (Banerji et al at poster discussion ESPMO 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 RECIST 1.1 and GCIG CA125. 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 0.01 5-sided level of statistical significance (or equivalently with 80% power at the 0.10 level of statistical significance), using a 3-outcome design. Secondary endpoints include objective response rate (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 and 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 (ORUK141442/52). Clinical trial information: ISRCTN16426935.

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TPS5611 Poster Session (Board #427), 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 outcomes (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, SWE, NOR), MITO (ITA); GECO (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/DGCC 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 high risk 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 all patients, 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), NOGGO (GER), BGOG (BEL), MaNGO (ITA), MITO (ITA), GECO (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: PHAEOMA. First Author: Yolanda 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 <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 PD-L1/ PD1 expressions. These factors make immune check point inhibitors 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. ENDPOINT: Objective tumour response. 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 ≥20% versus ≤5% (uninteresting rate) using therapy design with 10% type 1 error rate and 90% power to distinguish a difference in observed OTRR of ≥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 (otr ≥12.5%). BIOPSEMENTS: Tumour tissue and serial bloods (5 time points) will be collected for translational research. PHAEOMA 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: ACTRN1261700106336.
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.
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 EGFIR 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 EGFIR inhibition, for HNSCC of oral cavity, hypopharynx, larynx, or oropharynx with >10 pack-years (pk yrs) use. Pts were stratified by EOGQ PG (0) and nodal stage (N0-2aN2b–3), and randomized 2:1 to A 40 mgq and placebo (P); tx continued for 16 m if tolerated, or until disease recurrence. The primary endpoint was DFS. Results: Of 603 pts planned, 617 were randomized, 411, P 206. Median age was 58yrs; 86% were male; 65% EOGQ PG 0; most had smoked (AP ex-smoker: 66.7%; current: 28.2%). Subsites (AP): oropharynx 53.5%; hypopharynx 21.2%; larynx 19.1%; oral cavity 9.1%. The majority had T3 or 4 (AP 70.68%) and N2 disease (67.63%). Accrual was halted for futility on interim 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 1.33 (95% CI 0.81–1.71), p = 0.48). The Table shows key subgroups. Median treatment duration was A 300.4 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 15% vs 23% for P; CRT did not improve DFS in arm A vs B, respectively. Median PFS was 4.4 mo in arm A and 6.1 mo 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: A vs B added to a standard platinum doublet improved response and DFS but not intake in first-line treatment of R/M HNSCC. The control arm in this study performed better than expected. Clinical trial information: NCT01345669.

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 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 prevalent (population-weighted) percentage 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 < 0.001). 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 HPV16/18/11 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.
Head and Neck Cancer

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 PREDICT-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 ’blandled’ 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 chemoradiotherapy (42% vs 57.5%, 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 63.5% 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 = 0.75; 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). Results: 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.

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/m² cisplatin every three weeks concurrently with radiotherapy. The investigational arm received cisplatin (80 mg/m² d1) and fluorouracil (800 mg/m² iv 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 locoregionally relapse-free survival (LRRFS) rates between two arms (OS: 88.2% vs 88.5%, P = 0.815; LRRFS: 94.3% vs 96.8%, P = 0.056). There were no grade 3–4 toxicities during RT. The most common grade 3–4 toxicity during NACT was neutropenia (9.6% vs 0.1%). 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 (OWW) cisplatin is accepted practice for locoregionally advanced nasopharyngeal carcinoma (LANPC). However, ETW and OWW were never prospectively compared in phase 3 clinical trials. This study is to assess the efficacy and toxicity profile of CCRT with ETW versus OWW 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/m² every 3 weeks for 2 cycles or cisplatin 40 mg/m² weekly up to 6 cycles concurrently with IMRT. 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 chemoradiotherapy (42% vs 57.5%, 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 63.5% 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 = 0.75; 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). Results: 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.

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/m² 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/m² weekly or 100mg/m² 3-weekly concurrently with radiotherapy. Primary endpoint was locoregional control (LRC); secondary endpoints included toxicity, compliance, 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/m² (IQR 180-210). In the 3-weekly arm, 143 pts (95%) received > 2 cycles, median cumulative cisplatin dose 300 mg/m² (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 Peredo, University of the Sunshine Coast, 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 60-66 Gy (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 ≥5 nodes or largest node > 3 cm) or high-risk primary (T3-4 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), 274 (88%) completed all 38 weeks of CRT, 99 (31%) CRT. CRT consisted of weekly cisplatin 40 mg/m² IV x 6 doses and carboplatin (AUC 2) every 3 weeks during CRT (2 concomitant doses) and then following CRT for 2 months. The FLRR difference between PORT and CRT was not statistically significant (p = 0.039). 12 (3.9%) experienced Grade 3/4 subcutaneous fibrosis; 2.5% RT, 3.8% CRT (p = 0.84). 134 (43%) experienced Grade 3/4 skin toxicity; 49% RT, 37% CRT (p = 0.50). There was a freedom from loco-regional relapse (FLRR) difference between patients randomly assigned to 60-66 Gy (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 ≥5 nodes or largest node > 3 cm) or high-risk primary (T3-4 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).

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.

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.

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. Patients were stratified to high-risk nodal (either extracapsular nodal extension, intra-parotid nodal disease of any size or number, cervical nodal disease with ≥5 nodes or largest node > 3 cm) or high-risk primary (T3-4 or in-transit metastases). Patients with both features were stratified to high-risk nodal group. Secondary objectives included disease-free survival (DFS), overall survival (OS) and acute & late toxicity (CTCAE V3).

Results: A total of 38 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 regardless of HPV status. At data cutoff, 9/11 responses were ongoing regardless of HPV status.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 (7th 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 N2 disease, the positivity of ECS modifies the treatment approach. The objective of this study is to evaluate the impact of ECS inclusion in the final pathological report of resected HNSCC cases. 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 neck dissection (ND). In 157 cases (13.8%) ND was performed because of the presence of ECS and in 752 cases ECS was not present (66.2%). The mean interval of 8.5 weeks (6-10). 596 patients (52.4%) had postoperative RT (n=525) or CHRT (n=71). Mean follow-up: 5.6 years (SD 4.9). Results: Of the 157 cases, ECS was reported in 78.2% of cases. ECS was present in 1184 cases (99.9%) and was not reported in 4 cases (0.1%). ECS was present in 120 cases (76.9%) in unilateral ND and in 58 cases (77.1%) in bilateral ND. The proportion of ECS was 70% of the resected tumor or lymph node tissue area occurred in 6/21 pts (29%). Baseline tumor biopsy specimens were PD-L1 positive (> 1% of tumor cells) in 11/19 (58%) evaluable samples and in 7/8 (88%) evaluable pathologic resected samples. A significant correlation existed between baseline PD-L1 expression on tumor cells and CT/PET response effect in these pts with a single dose of pre-operative pembrolizumab. Further evaluation of this strategy is warranted. Clinical trial information: NCT02296684.

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 chemotheraphy (CT) and RT: Results of the GORTEC 2004-01 randomized trial. First Author: Jean Bourhis, Centre Hospitaller 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. 15.1% of pts had stage IVa (73%) vs 72%). All initial characteristics were well balanced between arms. The median follow-up was 4.7 years, different between arms. Acute and late xerostomia were markedly improved in arm A (IMRT arm). The 1-year grade 0-1 salivary toxicity (RTQoL) 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=0.65). 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: NCT0158678.
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, Universitätssklinikum 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 randomised 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 IV on days 1-5 and 29-33) (standard arm A) versus 63.6 Gy with intensified chemoradiotherapy 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 results. 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 16 months (range 3–45). 34% of pts were current or former smokers; 43% with recurrence within 6 months of completion of CRT treatment; 27% with prior exposure to EGFR inhibitors. Median PFS was 4.6 vs. 6.0 months for the P and E groups, respectively (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.42-0.95, p = 0.026). Benefits from E on PFS and OS were more pronounced in pts with oropharyngeal tumors (p<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 (39.9 vs. 33.3%, including diarrhoea 13% vs. 5%, dehydration 5% vs. 15%, nausea 5% vs. 14%, rash vs. 12%). Conclusions: This regimen may warrant further evaluation in randomized, phase 3 trials. Clinical trial information: NCT01126216.

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 randomised, 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 after failure 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 (240 mg IV Q2W) or IC. Pts in the IC group received IC as PR or adjuvant therapy. Results: 92 pts were allocated to 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% vs. 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 = 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: CRIT1/2015/06/005848.
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: Christophe Le Tourneau, Institut Curie - Centre de Lutte Contre le Cancer (CLCC) de Paris, Paris, France

Background: In CheckMate 141, nivo resulted in significantly prolonged overall survival (OS), favorable safety, and stable quality of life in ICs (pts) with platinum-refractory (PR) R/M SCCHN. Cetuximab, a flatiron 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 (NCT02015636) in which pts (N = 361) with PR R/M SCCHN were randomized 2:1 to nivo (3 mg/kg q2w) or IC, 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 <1% regardless of prior cetuximab, and in pts with PD-L1 expression <1% without prior cetuximab.

<table>
<thead>
<tr>
<th>Without Prior Cetuximab</th>
<th>With Prior Cetuximab</th>
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<tbody>
<tr>
<td>Median OS (95% CI), mo</td>
<td>(n = 147)</td>
</tr>
<tr>
<td>Nivo</td>
<td>17.2 (13.7, &gt;50)</td>
</tr>
<tr>
<td>IC</td>
<td>13.2 (10.5, 16)</td>
</tr>
<tr>
<td>Median PD-L1 expression</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Nivo</td>
<td>13.0 (9.0, &gt;50)</td>
</tr>
<tr>
<td>IC</td>
<td>10.9 (8.0, &gt;50)</td>
</tr>
<tr>
<td>ORR among pts with PD-L1 ≤ 1%</td>
<td>76.4 (61.0-91.0)</td>
</tr>
</tbody>
</table>

PFS was similar regardless of prior cetuximab, and the magnitude of benefit was greater in pts without cetuximab exposure. These results support the use of nivo for R/M SCCHN regardless of prior cetuximab use. Clinical trial information: NCT02105636.

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/MEK/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 12 months prior to randomization 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 RECIST v1.1 every 2 months. Primary endpoint was objective response rate (ORR) (complete- partial- 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, 55 pts (median age 63 years, 39 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 findings in melanomas 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.

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 V600E-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 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 PO BID) + T (2 mg QD) until unacceptable toxicity, disease progression, or death. Eligible pts had advanced ATC, PS 0-2, and adequate organ function. Doses were escalated to 150 mg PO BID and 3 mg PO qd. Cross-over to B was allowed at time of progression. Responses were assessed by RECIST v1.1. 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 ≥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 infrequent 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 79 histories. 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 V600E–mutated ATC. Clinical trial information: NCT02034110.
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). 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 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 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 2nd 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.

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 another single-agent therapy (docetaxel, cetuximab, or methotrexate) for patients with R/M SCCHN. Transition probabilities including disease progression, survival, and treatment toxicities were derived from clinical trials (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.

An open-label, multicohort, phase II/III study to evaluate nivolumab in patients with virus-associated tumors. First Author: Jean-Pierre Delord, Toulouse University Cancer Institute IUCT-Oncolep, Toulouse, France Background: Treatment options for patients (pts) with R/M NPC are limited to palliative chemotherapy. Nivolumab 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, 86% 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 the disease. Updated efficacy and biomarker data will be presented. Clinical trial information: NCT02488759.

Induction gemcitabine cisplatin followed by chemoradiation in locally advanced nasopharyngeal carcinoma. First Author: Sadaf Usman, Shaubuk 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 (LY) is an 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, 500 patients (M 70%; F 30%) with histologically confirmed nasopharyngeal carcinoma. Histological subtypes WHO I 4% (13) and WHO III 96% (287). AJCC (7th edition) stage was Stage III 28% (85) and Stage IV 72% (215) patients. IC included a 2 drug combination; intravenous gemcitabine 1000 mg/m² on day 1 and 8 and cisplatin 75 mg/m² 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/m²) 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 investigations in randomized clinical trials.
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: Chang 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: Nimotuzumab 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 (200mgiv) and cisplatin (100mg/m², day 1) plus fluorouracil (4g/m², day 1-4) every 3 weeks until progressive disease (PD) or unacceptable toxicity or a maximum of 6 cycles. If patients had not progressed at this stage, Nimotuzumab (200mgiv) as monotherapy would be delivered until PD. This study was registered in ClinicalTrials.gov, Number NCT01161649. 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 who had 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 > 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: NCT01161649.

Efficacy and toxicity of Nimotuzumab combined with cisplatin plus fluorouracil (PF) in patients with metastatic nasopharyngeal carcinoma treated with neoadjuvant chemotherapy followed by concurrent chemoradiotherapy. 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 patients with 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 LRFS, DMFS and OS in NACT and CCRT were 94.5%, 96.8%, 85.8%, 82.6% and 81.6%, 83.4% respectively (<0.05). For stage III patients, the 3-year LRFS, 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–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 = 0.011). 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A phase I clinical trial of amcasertib in combination with docetaxel in borderline resectable head and neck squamous cell carcinoma (HNSCC). First Author: Eduardo Mendez, Department of Otalaryngology; 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/IV 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 as alone 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 m2). Tumors were sequenced with UWOncoPlex (262 cancer genes); HPV status assessed via p16 IHC; toxicities graded with RECIST, but SD by pathology and 1 had PD. TP53 wt/HPV-); 4 had PR (all TP53 mutants); 1 (TP53wt/HPV-) had a PR by RECIST, but SD by pathology and 1 had PD. 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 100 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 response rate (ORR, proportion with partial PR) or complete response (CR) per RECIST was 13% and the disease control rate (DCR, proportion with stable disease (SD) or PR) 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.

Poster Session (Board #22), 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 100 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 response rate (ORR, proportion with partial PR) or complete response (CR) per RECIST was 13% and the disease control rate (DCR, proportion with stable disease (SD) or PR) 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.

Poster Session (Board #20), 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 radiotherapy (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. Results: For patients with untreated HNSCC, we identified 3,516 patients treated 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 vs 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 vs 11.2 months) and 5-year (17% vs 7%) OS compared to chemotherapy alone (log rank, p < 0.001). 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 Gy10 was associated with prolonged survival (median 12 months 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.

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A phase 1b/2 study of amcasertib, a first-in-class cancer stemness kinase inhibitor, in advanced adenocystic 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 adenocystic carcinoma (ACC). An RP2D expansion cohort was opened for patients with ACC. Methods: Pts with metastatic, unsecteateble 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.

A phase II multi-centered trial of the multitargeted kinase inhibitor sulfatinib in advanced medullary thyroid cancer (MTC) and radiodine (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 study enrolled 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 other 3 responses were 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%), hypertension 50.0% (Grade 3-4: 0%), hypertension 44.4% (Grade 3-4: 16.7%), blood bilirubin increased 44.4% (Grade 3-4: 18.7%), 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 with previous report, with mostly manageable AEs. Efficacy is encouraging in both indications. Further investigation is warranted. Clinical trial information: NCT02614495.
A retrospective cohort study of PD-L1 expression in recurrent and metastatic squamous cell carcinoma of the head and neck (SUPREME-HN).

**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. CNO was determined by a negative neck CT or MR scan. Exclusions included non-SCC, non-surgical candidates, skin, non-opharynx 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 non-parametric 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 generalization assumption among the oncology community that PET/CT had a high NPV. Therefore, patients sent to study centers for 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/synthetic 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**

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Two-year clinical outcomes of de-intensified chemoradiotherapy for low-risk HPV-associated oropharyngeal squamous cell carcinoma. First Author: Bhishajjit 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, NO-N2c, MO, HPV or p16 positive, and minimal smoking history. Treatment was limited to 60 Gy intensity modulated radiotherapy with concurrent weekly intravenous cisplatin (30 mg/m²). 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 (EDORT 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, 86% > / = 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 (stoke and glioblastoma). Mean pre and 2-year post EDORT 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 0.40±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.

HPV status and survival in non-oropharyngeal squamous cell carcinoma of the head and neck. First Author: Vanessa Wooley, 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 and compare survival differences at each timepoint. 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), primary 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 at 1 year (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.
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 87,26 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 0.60-0.8, P = 0.01). A univariate and multivariate analysis were performed adjusting for age, sex, race, stage, primary site, Charlson/Deyo comorbidity index, income, financial income, tumor grade, 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 patients 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.

**Results:**

- **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 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 CD28+ 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+ TIM3+ 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+ Treg 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 CD28+ T cells and CTLA-4+ CD8+ effector T cells, and lower PD-1+ CD8+ effector T cells 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 Tregs expressing both checkpoint receptors. Clinical trial information: NCT02105636.

**Conclusions:**

- **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 CCD. Candidate biomarkers in inflamed HNC patients were de-identified and expression of MAN with anti-PD-1. **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 explore 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 leucocyte 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 CA182661-01A1 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 assessed pre- and post-treatment biopsies from anti-PD1 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-PD1 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 predictors 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 type was redefined using the ATHLATES algorithm. Haplotype distribution of allele and haplotypes of classical HLA genes (A, C, B, DRB1 and DBQ1) 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–DBQ1 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 = 1.25–4.93). 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–DBQ1 haplotype 04:01–03:01 in the general African American population is significantly lower. Conclusions: DRB1–DBQ1 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–DBQ1 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, Chronic 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. Patients were stratified into control 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-PD1 monotherapy. The results provide rationale for combinatorial therapies targeting the IDO1 and PD-1-PD-L1 networks in HNSCC patients.

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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-25a, 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 = 0.029) 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 +)). 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 < 0.001 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 = 0.026) and OS (p = 0.009). 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 CA182661-01A1 to NFS and GZC).

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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 93 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 12.6 months and 49.0 months respectively (P = 0.022). 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 = 0.022). Conclusions: CDKN2A copy number loss was associated with poor survival in HNSCCs stratified by HPV status. CDKN2A copy number loss as a relative log2 copy number ratio ≤ −0.6, CDKN2A mRNA and p16 protein expression, with poor prognosis in terms of disease-free and overall survival.
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 400, including 300 T1 and T2 cases. Patient acceptance was 89%. Median follow up is 3 years. The primary endpoint is 1 year. The 2-year PFS and OS were both 100% for low-risk pts, and 91.5% and 97.0% for higher risk. Significant decrease in the rates of grade $\geq 3$ mucositis (15.8% RT50, 46.4% CRT45, 60.0% CRT75, $p = 0.033$) and grade $\geq 3$ dermatisis (0% RT50, 21.4% CRT45, 30.0% CRT75, $p = 0.056$) was observed. PEG-tube dependency was improved at 3 months (0% RT50, 14.8% CRT45, 70.0% CRT75, $p < 0.001$) and 6 months (0% RT50, 3.7% CRT45, 20.0% CRT75, $p = 0.066$) post-treatment.

Conclusions: Favorable response to induction chemotherapy appears to be a biomarker for better outcome and volume of disease resection. Lugol’s Iodine 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 advanced OPC (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.

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 ± 0.85). There were 696 (mean 3.74 ± 3.22) office visits among 186 pts and 367 (mean 3.95 ± 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 ± 1.54), 137 (mean 1.67 ± 1.19) and 118 (mean 1.4 ± 0.78) visits for 114, 82 and 84 pts, respectively. CT scans (286), lab tests (418), x-rays (180) and other tests (400) were ordered in 136, 180, 120 and 194 pts, respectively. Three pts were institutionalized for end of life care (mean 28 days = 26.06), and 214 pts were hospitalized (mean 14.5 days = 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.
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: Yungian 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/35F7 weeks. Concurrent chemotherapy was 3 cycles of carboplatin-SFU 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- (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.
Methods: reduction in radiation (RT) to 30Gy with concurrent chemotherapy in patients associated oropharynx cancers (OPC).

Background: HPV HNC pts are younger and have a higher cure rate than smoking-related pts, 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: 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 12mo when comparing low dose IMRT vs. 3DRT (65% vs. 33%. p = 0.057). No other statistically significant reductions in toxicities 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 Katf, 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 of technique as well as IMRT dose, and will therefore be utilized in future ECOG-ACRIN HNC studies. Clinical trial information: NCT01084083.

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, 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: 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 12mo when comparing low dose IMRT vs. 3DRT (65% vs. 33%. p = 0.057). No other statistically significant reductions in toxicities 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 Katf, 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 of 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 #65), 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 PSQHN, 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. The 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 of the other pats 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 pilots 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 2015-2016. Primary tumors were excised and analyzed for DNA repair foci ex-vivo. A pre-RT dynamic 18F-FMISO (fluoromisonidazole) PET was then used to assess hypoxia (defined as >1 tumor to muscle SUV ratio). Conclusions: Both cervical lymph nodes. Patients without hypoxia on baseline or repeat scan done 5-10 days after initiation of chemorRT received 30Gy (57% reduction) over 3 weeks to the tumor bed and neck with 2 cycles of concurrent chemotherapy (50% dose reduction) and anti-emetics. The total standard dose of 70Gy over 7 weeks with chemio. Neck dissection (ND) was done 4-months post chemorRT. Weekly DWI MRI, CDNA, 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 18F-FMISO scans, 13 were positive and 6 were negative for hypoxia. Of the 12 intra-treatment 18F-FMISO scans (1 not done due to intermittent illness, this patient received 70Gy, 3 were positive and these patients received 70Gy chemorRT. 15 patients were de-escalated to 30Gy. To date, analysis showed complete pathologic response in 8 of 9 patients (all expected to have ND by April 2017). The one positive case received only 1 cycle of cisplatin. To date, 18 of 19 patients (95%-86% of 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 a personalized approach to a major decrease in RT dosing for definitive treatment of HPV+ oropharynx 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: NCT00602594.
**Poster Session (Board #66), Mon, 1:15 PM-4:45 PM**

**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 radionanthers, 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 destroy the cells and possibly improve the 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%, and 15% (11 pts) and 70Gy or 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 hernorrhage (1 pt). Results demonstrated that a single injection of NBTXR3 provides adequate biodegradability 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 ≤ 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.

**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 (IMRT) in combination with cetuximab**

**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. BLY719 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 BLY719 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 treated with cetuximab and nimotuzumab 400 mg/m² IV loading dose prior to intensity modulated radiation therapy (IMRT), followed by 250 mg/m² weekly infusions during IMRT. BLY719 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. 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 ≤ 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.

**Poster Session (Board #68), Mon, 1:15 PM-4:45 PM**

**A phase I 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:** 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 lifelong 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:** Nineteen pts 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, 2nd and 3rd 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 chemoradiotherapy due to grade 3–4 acute mucositis and leukocytopenia were 10.9% and 9.3%, respectively, with no cases of skin rash and infuion 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.

**Poster Session (Board #69), Mon, 1:15 PM-4:45 PM**

**A phase I study of cetuximab + BLY719 + IMRT in stage III-IVB head and neck squamous cell carcinoma (HNSCC)**

**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 pts were retrospectively enrolled. They were 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 neoadjuvant chemotherapy were related to 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.
Average activity of RAI, median cumulative activity of RAI, determined using the 80th percentile of the number of cases treated per calculated, and the threshold for distinguishing high volume vs. low volume was (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, ACC, ACC, or A and were included in the analysis. There were 6534 patients treated in LV (41%) and 9839 in HV (59%). CV centers were more likely to be academic and integrated network cancer programs (p < .001). The median age for LS vs. HV was 61y vs. 58y (p < .001), 49% vs. 55% were male, 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 (55% vs. 47%), respectively, within the neck (72% vs. 64%, p < .001), and longer hospital stays (mean 2.21 days vs 1.55 days, 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 (1m 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 SG 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.

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Poster Session (Board #71), Mon, 1:15 PM-4:45 PM
RNAseq analysis of the soraferbin 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, soraferbin significantly impacted progression-free survival (PPS) 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 histotypes. 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). 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 (p < 0.05) between 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
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 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 (27%); prior tyrosine kinase inhibitor – 9/15 (54%). There was one DLT - Grade 5 event likely unrelated to drugs in a pt with ATC. Grade 4 toxicities – 0. Grade 3 toxicities – partial response rate is evaluable. 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.

6082
Poster Session (Board #70), Mon, 1:15 PM-4:45 PM
Interim baseline characteristics from the 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. Bruse, 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: 274 patients were enrolled on the phase I portion of the study. Gender – 10/15 (54%). There was one DLT - Grade 3-LAP 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 (27%); prior tyrosine kinase inhibitor – 9/15 (54%). There was one DLT - Grade 5 event likely unrelated to drugs in a pt with ATC. Grade 4 toxicities – 0. Grade 3 toxicities – partial response rate is evaluable. 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Targeted therapy for advanced salivary cancer with HER2 or hedgehog alterations: Interim data from MyPathway. First Author: Rassele Kurucz, 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 the 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 tumors 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 (SMM 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 6.6 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.

Comprehensive genomic profiling of parathyroid carcinoma. First Author: Hyeunseok 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 PRUNEL2 in a limited number of patients. We queried whether comprehensive genomic profiling (CGP) would have potential to discriminate PC subtypes and select 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 62x for up to 315 cancer-related genes plus 37 in 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 mechanistic 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%). Most frequent CRGA were KDR (23%), KEAP1 (23%), and TERT (23%). Frequent alterations in genes controlling cell cycle progression at G1 including CDKN1B, CDKN2A, CDKN2B and CDK4 were identified (30%). The most frequent CRGA involved Pten (23%), Nf1 (23%) and Kdr (15%). No alterations in BRCA1 were identified. A patient with KRD mutation treated with cabozantinib experienced >50% drop in PTH 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.
Methods: LA-HNSCC. HNSCC. CRT has immunomodulatory effects; preclinical data suggest that 60% of patients. The PD-l inhibitor pembro is approved for recurrent/metastatic 

Background: Approximately half of patients (pts) with HNSCC are diagnosed with locally advanced disease and treated with surgery or concomitant chemoradiation (CRT) with cisplatin. Unfortunately, disease recurs in 40% to 60% of patients. The PD-l inhibitor pembro is approved for recurrent/metastatic 

Methods: Adult pts with newly diagnosed, pathologically proven, treatment-naïve LA-HNSCC will be enrolled. Study population will include p16-negative HNSCC (any T3-T4 or any N2-N3 (AJCC 7th edition)) and p16-positive oropharyngeal cancer (any T4 or any N3). Other eligibility criteria: measurable disease per RECIST 1.1 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/week] or standard [70 Gy, five 2 Gy fractions/week fractionation]) plus cisplatin 100 mg/m² 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 MR I 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, every 4 months during the next 2 years, and then every 6 months after CRT. Dissection will be performed by neck dissection determined by clinical and radiological assessment 3-months post treatment. (3) IMRT 64 Gy in 25 F + cisplatin 100 mg/m² day 1 of week 1 and week 5 or weekly 40 mg/m² +/- neck dissection as per standard treatment. (4) Resection of primary + selective neck dissection followed by standard treatment. (5) One cycle of induction durvalumab 1500 mg followed by standard treatment then durvalumab 1500 mg every 4 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. ISRC Number: 41478539, CRUK CRUK/13/02 Clinical trial information: 41478539.

Methods: Patients with intermediate and high-risk oropharyngeal cancer (OPC) who are treatment-naive at 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 CRT 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 ≥ 10 pack years 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 5-weekly cisplatin 100 mg/m² or weekly 40 mg/m² with intensity Modulated Radiotherapy (IMRT) using 70 Gy in 35 F +/- neck dissection determined by clinical and radiological assessment 3-months post treatment. (3) IMRT 64 Gy in 25 F + cisplatin 100 mg/m² day 1 of week 1 and weekly 40 mg/m² +/- neck dissection as per standard treatment. (4) Resection of primary + selective neck dissection followed by standard treatment. (5) One cycle of induction durvalumab 1500 mg followed by standard treatment then durvalumab 1500 mg every 4 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. ISRC Number: 41478539, CRUK CRUK/13/02 Clinical trial information: 41478539.

Methods: Head and Neck Cancer

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. Mackiels, 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 chemoradiation (CRT) with cisplatin. Unfortunately, disease recurs in 40% to 60% of patients. The PD-l inhibitor pembro is approved for recurrent/metastatic 

Methods: Adult pts with newly diagnosed, pathologically proven, treatment-naïve LA-HNSCC will be enrolled. Study population will include p16-negative HNSCC (any T3-T4 or any N2-N3 (AJCC 7th edition)) and p16-positive oropharyngeal cancer (any T4 or any N3). Other eligibility criteria: measurable disease per RECIST 1.1 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/week] or standard [70 Gy, five 2 Gy fractions/week fractionation]) plus cisplatin 100 mg/m² 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 MR I 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, every 4 months during the next 2 years, and then every 6 months after CRT. Dissection will be performed by neck dissection determined by clinical and radiological assessment 3-months post treatment. (3) IMRT 64 Gy in 25 F + cisplatin 100 mg/m² day 1 of week 1 and weekly 40 mg/m² +/- neck dissection as per standard treatment. (4) Resection of primary + selective neck dissection followed by standard treatment. (5) One cycle of induction durvalumab 1500 mg followed by standard treatment then durvalumab 1500 mg every 4 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. ISRC Number: 41478539, CRUK CRUK/13/02 Clinical trial information: 41478539.

TPS6091 Poster Session (Board #78b), Mon, 1:15 PM-4:45 PM

TPS6092 Poster Session (Board #78c), Mon, 1:15 PM-4:45 PM

TPS6093 Poster Session (Board #78d), 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) compared to placebo + CRT. 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 ≤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/m² [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, 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 predefined stopping criteria for withdrawal occurs. Enrollment in this phase 3 trial began in November 2016. Clinical trial information: NCT02952586.

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Head and Neck Cancer

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: Pietruigi 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 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 q2.12 Gy tx in 33 fractions over 7 weeks) with concurrent CTX (400 mg/m² 1 week before RT start followed by 250 mg/m² 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) assumed to be 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 (α = 0.1, power is 0.80 when the 2-year PFS is ≥78%). The required sample size with this design is 69 patients. Patients affected by high-risk (> N2a or > T3, any N) larynx, hypopharynx and HPV negative oropharynx or HPV-positive oropharynx (> N2b, > 10 packyears) 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 1st line recurrent/metastatic disease settings, the ultimately the biggest potential impact based on patient outcome 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 ≥20% at 2 years. The primary endpoint is the 2 year progression free survival (PFS) rate, compared to placebo. A sample size of 94 (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 I (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 Payne, 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 PD-L1 may act as a negative regulator of the adaptive immune response and T-cell exhaustion. In addition, O may complement the antitumor activity of D. Methods: OPHelia is an open-label randomized multicenter phase I (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 600mg daily for 21-28 days (12 pts), cisplatin 60 mg/m² on day 1 followed by 0.75mg 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 18F-fluorodeoxyglucose (FDG-PET/CT) scans are obtained at diagnosis and at study 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 (CTC) evaluated for DNA 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 ipilimumab (Ipi) concomitant with (C) RT in intermediate (IR) and high-risk (HR) head and neck squamous cell carcinoma (HNSCC) (RTOG 3504, NCT02764593). First Author: Laura G. 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 I/II trial was designed to investigate the hypothesis that Nivo has additive activity as part of CRT when administered to patients with high-risk HNSCC. Methods: Eligibility includes: IR HNSCC (p16+, oropharynx T1-2N2b-N3/T3-4N0-3, > 10 pack-years (pts) or T4N0-4s, T3-1N3-3s > 10 pts) and HR HNSCC (cervix, larynx, hypopharynx, T3-4N0-3). A safety run-in will be undertaken 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 ≥20% at 2 years. The primary endpoint is the 2 year progression free survival (PFS) rate, compared to placebo. A sample size of 94 (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.

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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.

Ribociclib and everolimus are tolerable based on Phase I/II trial results in the latest arm of the biomarker/oncogene directed 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 overall survival; 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.

**Methods:** The combination of everolimus and ribociclib targets mutations/abnormalities that are frequently seen in ATC, and is tolerable based on Phase III 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 survival 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.**

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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 therapies 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 ≥10% 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 immusuppressive 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.

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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 (CanDecide), 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.

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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 9/1/14 to 3/1/16. Upon admission, we used the Edmonston 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: 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 pain (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 < 0.003). Patients discharged to hospice vs. PAC had lower 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) and have impaired mobility (OR 2.69, 95% CI 1.59-4.61, p < 0.0001). Conclusion: 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.

Diagnoses Codes

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pp + PpChronic + others</td>
<td>$1,448</td>
</tr>
<tr>
<td>Pp + no PpChronic + others</td>
<td>$2,134</td>
</tr>
<tr>
<td>no Pp + PpChronic + others</td>
<td>$1,211</td>
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<tr>
<td>no Pp + no PpChronic + others</td>
<td>$1,590</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

Costs were adjusted to $2016.
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% opted rapidly (despite delayed), and 3% of patients decided against recommendations. Forty-four (44) percent were screened for recommendations were followed in 70% of cases, 16% continued current/other time to review request was 15 days from receipt of results. MTB recommended clinical trials in 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 for both mRCC (OR: 1.23, 95% CI 1.13-1.33, mean payments $185,763). Results: Mean payments $33,391) but not CML (OR: 1.10, 95%CI 0.83-1.45, mean payments $566) and CML (OR: 1.29, 95%CI 1.13-1.48, mean payments $185,763). Conclusions: Receipt of general payments from oncologists was 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 rating in the context of the NCCN EB framework. 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 EBs, answering the following questions: per patient both in and 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 $178 (OR: 1.78, 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.
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 5/5/2012 & 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, and social service referrals for only 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 the clinicians. Only 25% of clinicians behaved confidently in how to address a patient’s 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 ways to improve existing conversations will be important to mitigating additional financial distress.

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, phase, type of outcome, and study design. Results: Among 139 trials in ClinicalTrials.gov database, 34 were selected for comparison. We identified 31 trials with matching primary publications from PubMed. A total of 151 publications were included, 59 (39%) of which were conference abstracts. Of the 59 abstracts, 25 (42%) presented complete results of the phase I trials. Conclusions: For phase I cancer trials reported in ClinicalTrials.gov, results from primary publications were incomplete and often not peer-reviewed. This is concerning given the importance in ensuring equitable geographic access to cancer clinical trials, and would be of even greater importance if the clinical trials database included more completed reports.
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 cancers 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 (12% for men vs. 13.2% for women; p < 0.001), but not for those tested for LS (25.6% 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.

Racial composition in trials supporting the U.S. approval of anti-cancer new molecular entities (NMEs): 2011-2016. First Author: Lola A. Fashoyin-Aye, U.S. Food and Drug Administration, White, 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 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 NHPI/AIAN patients enrolled in the US while the majority of AA and NHPI/AIAN patients were enrolled from the US.

Comparison of comorbidity measures to predict postoperative lung cancer survival in the National Cancer Database (AFT-03). First Author: Melissa L. White, Division 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 data sheets. However, the prognostic performance of this code-based CCI has not been compared with a medical chart-based CCI or individual comorbidity conditions in a nationally representative sample of patients with lung cancer. Methods: Through a special study of the NCDB, cancer registrars performed a chart abstraction for 18 periperaoperative comorbidity conditions for 9,640 randomly selected patients with stage I-II 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+), and special study chart-based continuous CCI, and individual comorbidity 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 CCI was 51.9% with the code-based CCI underestimating morbidity for 36.2% patients. The model including individual comorbidity 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 included as important in their decision-making process. Improved understanding of these differences may provide opportunities to address racial disparities in prostate cancer. Factors influencing prostate cancer treatment decisions for African American (AA) and Caucasian (CA) men. First Author: Brittany-Belle Elizabeth Gordon, University of North Carolina, 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%, respectively. Conclusions: AA and CA men with prostate cancer are both concerned about curing cancer, 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.
Cancers of the Breast and Prostate: Impact of the Affordable Care Act (ACA) on Treatment Approaches, Outcomes, and Financial Burden

Jennifer L. Gold, Carrie E. Berg, Sarah J. Olszewski, Jane K. Sapp, Brett D. Flaschentrager, Alpert Medical School of Brown University, Providence, RI

Background: The Affordable Care Act (ACA) implemented in 2014 has substantially increased insurance coverage for Americans 18-64 years old. After the implementation of the ACA, we examined: (1) the impacts of ACA on breast and prostate cancer treatment approaches and outcomes; and (2) the impacts of ACA on patients' financial burden including the impact of patient responsibility for out-of-pocket (OOP) costs. Methods: Using SEER-Medicare data, we identified patients diagnosed with breast cancer between 2006 and 2014 and patients with prostate cancer diagnosed between 2006-2013. The study period was divided into 2 periods: pre-ACA (2006-2010) and post-ACA (2011-2014). We analyzed patients' receipt of surgery, radiation, and chemotherapy for breast and prostate cancer. We used multivariable logistic regression models to examine: (1) the ratio of treatment approaches between the pre-ACA and post-ACA periods, and (2) the ratio of patients' OOP costs between the pre-ACA and post-ACA periods. Results: The ACA increased the use of surgery and decreased the use of radiation for breast cancer. For prostate cancer, the ACA increased the use of radiation and decreased the use of surgery. Regarding OOP costs, the ACA was associated with a 30% decrease in the median OOP cost for breast cancer surgery and a 10% decrease in the median OOP cost for prostate cancer radiation. Conclusion: The ACA has impacted both breast and prostate cancer treatment approaches and OOP costs. Further research is needed to evaluate the financial burden associated with cancer care.

ASCO A4406: Health Services Research, Clinical Informatics, and Quality of Care

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

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. 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 40-79 years, 93,688 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 was observed to increase significantly for female breast cancer (PR = 1.09 [95% CI 1.01-1.18]), colorectal cancer (PR = 1.15 [95% CI 1.07-1.24]), prostate cancer (PR = 1.14 [95% CI 1.06-1.23]), and lung cancer (PR = 1.20 [95% CI 1.11-1.30]). A shift to stage I disease was also observed for cervical cancer (PR = 1.16 [95% CI 1.06-1.27]), although not statistically significant. In contrast, the percentage of stage I disease for prostate cancer (18.5% vs. 17.2%; PR = 0.93 [95% CI 0.90-0.96]) 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 recent US Preventive Services Task Force recommendations against routine prostate cancer screening.

ASCO A4407: Health Services Research, Clinical Informatics, and Quality of Care

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

Closures of Medicare Part D coverage gap by the Affordable Care Act (ACA) and use of oral anti-myeloma immunomodulatory drugs (IMiDs)

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 propensity-weighted mixed Cox proportional hazards regression strata by subtype. Pre-ACA and post-ACA periods were identified by cost sharing changes for Low Income Subsidies (LIS) are exempt from cost sharing, and LIS is associated with a 50% manufacturer discount on the price of brand-name drugs within the 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 40-79 years, 93,688 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 was observed to increase significantly for female breast cancer (PR = 1.09 [95% CI 1.01-1.18]), colorectal cancer (PR = 1.15 [95% CI 1.07-1.24]), prostate cancer (PR = 1.14 [95% CI 1.06-1.23]), and lung cancer (PR = 1.20 [95% CI 1.11-1.30]). A shift to stage I disease was also observed for cervical cancer (PR = 1.16 [95% CI 1.06-1.27]), although not statistically significant. In contrast, the percentage of stage I disease for prostate cancer (18.5% vs. 17.2%; PR = 0.93 [95% CI 0.90-0.96]) 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 recent US Preventive Services Task Force recommendations against routine prostate cancer screening.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

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 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.

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

Methods: This was a descriptive study analysis of all new hematology/oncology cancer indications assessed by HAS between 2010 and 2015 has been conducted. For each indication, using evidence from published studies. We assessed the re-spective study analysis of all new hematology/oncology cancer indications assessed by HAS between 2010 and 2015 has been conducted. For each 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 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.
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 evit. 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% evit. 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 evit 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 steps to publish and 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 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.

Results: Of 737 potential respondents, 420 (57%) responded; 16% had heard of chemotherapy shortages (31% vs 14%, p = 0.03), as were those with greater awareness (p = 0.01). Most desired to be informed about a chemotherapy substitution if such data would affect their treatment decisions. Steps would include potentially informing the general population of on-pathway treatment, pathway vendors should take

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 those with one or more comorbidities (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.
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 Database Data. Insurance status was categorized as Private, Medicaid (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.

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), stage I (OR 2.68; CI 2.43-2.96 p < 0.0001), stage II (OR 2.86; CI 2.61-3.12 p < 0.0001), and stage III (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 1.52; CI 1.52-1.55 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 1.6; 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.
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 present 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=20); 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

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<td>MYC Rearrangment (%)</td>
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Conclusions: Reasons for non-enrollment included: 1) Protocol ineligibility (n=58); 2) Physician choice (n=20); 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.

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 significant 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: 26,943 patients initiated chemotherapy 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 0.84 and 0.88, 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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, 0.87-0.8) 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, 0.77-0.92). 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.
Exploring the time delay between regulatory approval and health technology 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 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.

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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 county’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 hosptices, 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 EORC TeleQ-LQC-CTO (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 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 grounded theory approach to abstract cares and a guide to 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 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.

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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 erasing 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 characterizations 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, 87% 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 network 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 (Odd’s Ratio 1.22, 95% Confidence Interval 1.03, 1.43). Conclusions: Physician 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 over-screening in cancer.

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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, QOL and QOH 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/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 = 0.35, p < 0.018), insured by Medicaid (OR = 3.22, p < 0.011), and were more likely to rate their QOL (OR = 3.76, p < 0.001) 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 disabilities need to assess financial stress in order to address this issue.

Most Commonly Tested Groups

<table>
<thead>
<tr>
<th>Age</th>
<th>1 Positive</th>
<th>2013 Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-45</td>
<td>19.6</td>
<td>25.0</td>
</tr>
<tr>
<td>45-64</td>
<td>8.4</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Least Commonly Tested Groups

<table>
<thead>
<tr>
<th>Age</th>
<th>1 Positive</th>
<th>2013 Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>65+</td>
<td>8.4</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Results: 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 widened interventions may help improve quality of care and equity in test receipt.

Background: Multidisciplinary tumor boards (MTBs) are commonly practiced in high-income countries 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. Guidelines 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 cancer cases, 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.
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 from 1.005 (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 eg, 5 yr OS for stage I NSCLC was 56% (±0.2) for TTI < 6 wks vs 43% (±0.2) for TTI > 6 wks and for stage I pancreas was 38% (±0.6) vs 29% (±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.

Survival by race among patients who received standard of care (77.8% of all patients).

<table>
<thead>
<tr>
<th>Race Group</th>
<th>No. of Subject</th>
<th>12 Mo Survival (95% CI)</th>
<th>60 Mo Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA/PA/Other</td>
<td>3234</td>
<td>93.1% (92.2%, 93.9%)</td>
<td>67.6% (65.7%, 69.5%)</td>
</tr>
<tr>
<td>AA</td>
<td>9749</td>
<td>91.1% (90.5%, 91.7%)</td>
<td>58.8% (57.7%, 59.9%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5233</td>
<td>93.3% (92.6%, 94.0%)</td>
<td>64.8% (63.2%, 66.3%)</td>
</tr>
<tr>
<td>NHW</td>
<td>46668</td>
<td>93.7% (93.4%, 93.9%)</td>
<td>66.0% (65.4%, 67.4%)</td>
</tr>
</tbody>
</table>

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 ≥ 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/ researchers.” Despite comorbidities, COPD, age and other demographic data, the OR for surgery 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). (Dykert et al JAMA 2010) A 3 year retrospective chart review of all patients with early stage NSCLC at the 3 academic institutions involved in the 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 demographics, a non-Hispanic White (NHW) was 7% more likely to have surgery than 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 treatment racial groups, especially between AA and C. 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.
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 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-low (2006-2009: 64.6% versus (vs) 2011-2014: 69.1%, p = 0.003) and high-income zip codes (80.4% vs 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.

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, which may reflect gaps in access to evidence of safety and efficacy.

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 bio marker 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, adjusting 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 (> 75y) (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.

Background: Disparities in prognosis communication among parents of children with cancer: The impact of race and ethnicity.

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 highest amongst White (51%) versus Black (28%) and Hispanic parents (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.

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 (3%) 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 NCI’s database, containing 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%), and Vietnam (10%). 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.
A Type of Research: 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 (8) 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 female = 75%). Results: Among Black PIs, 38% (vs. 50% for W) responded. Conclusions: These results underscore the need to address race and sex-related issues in the mentorship network of cancer researchers.

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Prospective assessment of psychosocial outcomes of contralateral prophylactic mastectomy. First Author: Abereaa 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.

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 (AEs) and hospitalizations with activity data. Multivariable regression models 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 (25%) 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. 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.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Hospitalizations</th>
<th>Overall Survival</th>
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<tbody>
<tr>
<td>Odds ratios (p-value)</td>
<td>Odds ratios (p-value)</td>
<td>Hazard Ratios (p-value)</td>
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<tr>
<td>------------------</td>
<td>------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Steps (per 1000 step increase)</td>
<td>0.36 (0.03)</td>
<td>0.23 (0.02)</td>
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<td>Stairs (per 10 stair increase)</td>
<td>0.59 (0.11)</td>
<td>0.44 (0.06)</td>
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<tr>
<td>Sleep duration (per 1 hour increase)</td>
<td>1.78 (0.1)</td>
<td>1.94 (0.09)</td>
</tr>
</tbody>
</table>

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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% 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 = 0.035; high OR 1.8, 95% CI 1.2 – 2.9, p = 0.008). 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: 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.

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 2nd line 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. Respondents were offered a 5-point Likert scale. They reported decision-making preferences, whether a doctor discussed the non-curative nature of PC, information about non-curative PC, and emotional well-being. We used 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. Recall of curability discussions were less likely to have accurate expectations (21% vs 48%; OR: 0.29, 95% CI, 0.07-9.7). 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 associations reflect misunderstandings, differences in belief, or expressions of hope.

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) ß = 0.205 (95% CI, -0.649 to 0.239), with emotional domain (n = 13) ß = 0.775 (95% CI, -0.048 to 1.598), and with global domain (n = 24) ß = 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.

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 Parik, 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 (17.2%) were admitted as weekend admissions. 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 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.
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/day, ECOG 1 was 1890 steps/day and ECOG 2 was 845 steps/day (p = 0.0021). Minimum steps/day correlated with BFI (r = -0.56, p < 0.01). 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.

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 0-20) with continuous and higher scores indicating greater distress. We created summed 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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>B</th>
<th>95% Confidence Interval</th>
<th>Standard Error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESAS Physical</td>
<td>0.10</td>
<td>0.04 to 0.17</td>
<td>0.03</td>
<td>0.003</td>
</tr>
<tr>
<td>ESAS Emotional</td>
<td>0.10</td>
<td>0.05 to 0.15</td>
<td>0.03</td>
<td>0.005</td>
</tr>
<tr>
<td>PHQ-4 Depression</td>
<td>0.68</td>
<td>0.15 to 1.20</td>
<td>0.27</td>
<td>0.011</td>
</tr>
<tr>
<td>PHQ-4 Anxiety</td>
<td>0.55</td>
<td>&lt; 0.01 to 1.09</td>
<td>0.28</td>
<td>0.0498</td>
</tr>
</tbody>
</table>

Inpatient hematopoietic stem cell transplantation with an increase in health care costs.
First Author: Achuta Kumar Guddadi, 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 national 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 autologous transplants, which 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 is expected to increase as elderly patients are being allowed to receive HSCT and represents a higher future demand for health care services.

<table>
<thead>
<tr>
<th>Year</th>
<th>Autologous transplantation</th>
<th>Allogeneic transplantation</th>
<th>s/p Transplant with GVHD</th>
<th>s/p Transplant with other complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>68.7%</td>
<td>40.4%</td>
<td>74.5%</td>
<td>34.3%</td>
</tr>
<tr>
<td>2011</td>
<td>73.8%</td>
<td>42.4%</td>
<td>79.5%</td>
<td>36.3%</td>
</tr>
</tbody>
</table>

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Cancer patients have increased risk of venous thromboses. Venous thromboembolism (VTE) is reported to be a leading cause of death among 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 per 100,000 individuals compared to those at or older than 65 years (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 younger than 65 years who have metastatic lung cancer. These patients may contribute towards greater morbidity and mortality associated with metastatic lung cancer in this subgroup.
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 LOIs, it was only 36% for unsolicited LOIs. Therefore, we analyzed all ETCTN LOI disagreement letters (DLs) for unsolicited LOIs to identify the major reasons for disagreement. Methods: A content analysis was conducted on DLs issued between March 2014 and March 2016 (N = 50). Two coders independently scored disagreement 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 disagreement 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 (35%); clinical data not adequately advanced (34%); and, 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 comparisons: 246 patients, comparing commercial, competing trial, and competing clinical trials. Conclusions: The reasons for LOI disagreement can be categorized and quantified. To increase transparency in the NCI ETCTN LOI review process, disagreement reasons for each LOI 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.

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 chemotherapy-induced nausea and vomiting (CINV) have been limited. The authors propose the following: serotonin 5-HT3 and 5-HT1A receptors mediate CINV; aprepitant blocks both 5-HT3 and 5-HT1A receptors; serotonin and aprepitant act complimentary to block CINV. In the current study, we explored these potential mechanisms in a murine system. Methods: C57BL/6 male mice (10-12 weeks old) were used. The mice were divided into 6 groups with 5-6 mice in each: saline (control), aprepitant, 5-HT3 antagonist, aprepitant + 5-HT3 antagonist, and treatment groups (aprepitant + 5-HT3 antagonist + 5-HT1A antagonist or 5-HT1A antagonist only). Aprepitant and 5-HT3 antagonist were given at 0.1 mg/kg and 0.1 mg/kg, respectively. Results: The results showed that aprepitant reduced CINV when compared to saline (p < 0.05). Aprepitant + 5-HT3 antagonist showed a significant reduction in CINV compared to aprepitant (p < 0.05). Aprepitant + 5-HT1A antagonist and 5-HT1A antagonist only showed no significant reduction in CINV compared to saline or aprepitant. Conclusions: These findings support the role of serotonin and aprepitant in the mechanism of CINV. They also suggest that serotonin and aprepitant act complimentary to block CINV.
Concordance assessment of a cognitive computing system in Thailand. First Author: Suthida Suwanwecho, Horizon Cancer Center, Bumrungrad International Hospital, Bangkok, Thailand.

Methods: 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. Concordance was attributable in part to local oncologists’ preferences for non-U.S. guidelines for certain cancers, especially gastric cancer. Conclusions: There was high 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, Somashekar 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.

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.

Methods: Chemotherapy (CM) 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 CM since 2005-2006. To evaluate the impact of US payment reform and guidelines on CM use at EOL, we estimated and compared the overall prevalence of CM 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 CM use at EOL for patients in all cancer groups. Two reviewers independently extracted data. Overall CM use prevalence was pooled by a random-effects model. Differences in prevalence of CM 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. CM use 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. CM 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. Conclusions: CM use near death is virtually unchanged over time. Effective interventions should be developed and provided to offset the trend of continuing CM use at EOL.

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.

Methods: 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 chi2 and Kruskal-Wallis tests. Results: We reviewed 1,047 hospitalizations of 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 emergency, acute clinical deterioration, and hypothetical discussions related to the futility of CPR. Transitions due to acute clinical deterioration were associated with less patient engagement and higher likelihood of inpatient death.

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Measuring cancer care experiences: Introducing SEER-CAHPS.

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 1993-2013 (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 prescriber/dispenser 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 205,539 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.

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Background: As cancer drug prices rise and insurance plans shift toward greater cost sharing, studies link patients’ high out-of-pocket (OOP) cost 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. Patiens 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.

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 of patients to treatment options. CGP may improve patient care and direct 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 diagnostic testing were evaluated and compared to cost and quality of care. Results were estimated using a decision-analytic model. The number of patients needed to test with CGP to add 1 life year was estimated. The 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 survival and a modest health plan budget impact, with most of the added costs attributable to increased use of effective treatments and prolonged survival.

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), to median overall survival (mOS), HR for disease progression (HR PFS), magnified 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 benefit compared to HR OS in Net Health Benefit calculations. 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 surrogate-derived CBS 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.
Methods: Kendall ICER, and NCCN frameworks to conduct value assessments of 15 drugs for breast, lung, and prostate cancer drugs were 0.560 (p=0.001), 0.950 (p<0.001), respectively. Pairwise, and subdomain W were 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: 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.
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 patients with available and investigational therapeutics. This study estimated anti-cancer 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 unmatched (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 (+$38k) (all p < 0.01); 66% of increased drug costs were attributable to longer time on treatment as opposed to higher monthly drug costs. Combination therapy was used for 71% of matched and 53% of unmatched patients. Those undergoing CGP in earlier lines (3; N = 58) vs. later line (4+; N = 130) therapy had numerically larger incremental increases in average time on treatment (+1.9 vs. +1.2 mos) and survival (+2.5 vs. +2.0 mos), and numerically lower incremental drug costs ($-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.

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 ($.8 billion) from cancer drugs would result from wastage in 2016. The pan-Canadian Oncology Drug Review (pCODR) committee proposes 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 to pCODR from 2012 to 2016 were reviewed 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 48.5%). When maximum wastage (i.e., the entire 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 5-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.

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 multi-modal 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 1.1 years in MMS groups. 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 through survey data from UKCTOCS. Expected outcomes from UKCTOCS were imputed to US values. Unit costs were updated to 2008 U.S.$. 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 included CA125, ultrasounds, clinical evaluations and false-positive surgeries, with an annual weighted cost of $35/3 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 vs. NS reduces mortality by $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 of 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.

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 RRM1; 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: Since VFs use 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.
6609 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 (k = 0.28, p = 0.002). When stratified by treatment intent (19 curative, 90 palliative RCTs), agreement remained poor (k = 0.23, p = 0.115; k = 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 high mean 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 (k = 0.12, p = 0.22); those meeting ESMO thresholds had a lower mean drug cost than those that did not (0.24, k = 0.346). Conclusions: There is only a weak correlation between ASCO and ESMO clinical benefit frameworks. Drug costs are not associated with ESMO/ASCO measures of magnitude of clinical benefit.

6610 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 (≥ 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 were 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 patients imaged 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 351.2. Conclusions: Surveillance imaging in asymptomatic patients beyond 2 years requires judicious consideration.

6611 Differences in medical care costs for recurrent versus de novo stage IV cancer by age at diagnosis. First Author: Matthew P. Banegas, Kaiser Permanente Northern California, Oakland, CA

Methods: Data from patients enrolled in three health plans who were diagnosed with de novo stage IV or 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 = 352; nrecurrent = 765), colorectal (n = 1072 and nrecurrent = 983), and lung cancer (n = 346; nrecurrent = 248) 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. Agreement between frameworks was fair at best (k = 0.28, p = 0.002). When stratified by treatment intent (19 curative, 90 palliative RCTs), agreement remained poor (k = 0.23, p = 0.115; k = 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 high mean 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 (k = 0.12, p = 0.22); those meeting ESMO thresholds had a lower mean drug cost than those that did not (0.24, k = 0.346). Conclusions: There is only a weak correlation between ASCO and ESMO clinical benefit frameworks. Drug costs are not associated with ESMO/ASCO measures of magnitude of clinical benefit.

6612 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 published clinical trials. Results: We identified 6 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.
Methods:
with implementation and compliance are essential for optimal execution. 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 affliations 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, near half stated their 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.

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 (Compensation for more Financially) in 2 sets of cancer patients. 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 (ESs) for independent FAC and their differences in FT in patients with cancer (grade 1, mild AE, 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.

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6617 Poster Session (Board #439), Mon, 1:15 PM-4:45 PM
Financial impact of flat dosed (FD) monoclonal antibodies (MBs) at a single institution in 2016. First Author: Michael P. Kane, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Immuno-oncology (IO) agents represent an important, accelerated breakthrough in cancer therapy. Like other MBs, these agents have been adjusted after FDA approval to be 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 pharmacokinetic 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 (Sing/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 IO/MBs may result in higher drug costs. Labeling IO/MBs with both weight-based and FD options and ensuring the availability of proper vials, particularly for small-dose vials, to fit the population and dosing schema would restrain the costs of care.

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 chemoinmunotherapy or observation alone. 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 RCHOP therapies. First-line RT strongly dominated observation, BR, and RCHOP. Compared with RT, 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 the cost-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.

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 and functional characterization is required for patient entry into clinical trials. Algorithms that encode complex clinical trial eligibility in a computable form have been developed. However, these tools are designed to match patients to clinical trials at single institutions. We have developed an open source computational platform that matches patients to multi-institutional precision cancer medicine trials. The software is available at https://github.com/dfci/matchminer.

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 RCHOP therapies. First-line RT strongly dominated observation, BR, and RCHOP. Compared with RT, 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 the cost-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.

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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 2003, 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 ($36,709 vs. $13,359 for CRC; $15,118 vs. $49,555 for LC), and 26-88% 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 ($28,796 for BC; $13,359 and $49,804 for CRC; $15,118 and $49,555 for LC), between groups. The primary drivers of spending differences between patients considering the 2 year-period spanning the diagnosis, spending was similar ($28,796 for BC; $13,359 and $49,804 for CRC; $15,118 and $49,555 for LC), 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 spending differences after diagnosis. Spending differences after diagnosis were driven largely by part B spending, which was due in part to differential chemo-therapy use.

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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

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 a Fitbit for at least 10 hour per day for ≥ 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, GRC/T unrestricted funding and TriValley SOCKS to MM. Clinical trial information: NCT03041545.
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 (TSS) requirements in patients (pts) with MF. This study was designed to test non-inferiority of MMB vs RUX in spleen volume reduction and Sx amelioration, and superiority in Tx requirement, in JAKi naive 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 dependence and platelets (<100, 100-200 and >200 K/μl).

Pts were randomized 1:1 to 24 wks of MMB 200 mg on + 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 spleen 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 dependence (T), 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 ≥3% occurred in 22% (10% of MMB and 10% of RUX) of Gr ≥3 (9% GR ≥2, 1 Gr ≥3) pts in DB phase, none continuing study drug for PN. Overall, AEs led to study drug D/C in 13% of MMB and 6% of RUX pts. In pts with JAKi naive MF, 24 weeks of MMB is non-inferior to RUX for spleen response but not for symptom response. Treatment emergent PN occurred in 22 (10%) of MMB (all Gr ≥3) and 10 (5%) of RUX pts. In previously RUX treated patients, 24 weeks of MMB was not superior to SRR; ≥35% reduction in volume from baseline).

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**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MMB</th>
<th>RUX</th>
<th>p-Value</th>
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<tr>
<td>Spleen response rate, %</td>
<td>20.5</td>
<td>29.0</td>
<td>0.011*</td>
</tr>
<tr>
<td>TSS response rate, %</td>
<td>28.5</td>
<td>42.2</td>
<td>0.98</td>
</tr>
<tr>
<td>Ti rate, %</td>
<td>66.5</td>
<td>49.3</td>
<td>&lt;0.001*</td>
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<tr>
<td>TD rate, %</td>
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</tr>
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<td>T relative rate/month, median</td>
<td>0.00</td>
<td>0.04</td>
<td>0.001*</td>
</tr>
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</table>

*Non-inferiority test; **Superiority test, all values nominally significant.

7002 Bousoutilis (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 in CML patients with Ph+ CML. Methods: In this ongoing, multinational, phase 3, open-label study, 536 patients (pts) with newly diagnosed CP CML were randomized 2:1 to BOS 400 mg QD vs IM 400 mg QD. Treatment emergent PN >3% occurred in 22% (10% of MMB and 10% of RUX) of Gr ≥3 (9% Gr ≥2, 1 Gr ≥3) pts in DB phase, none continuing study drug for PN. Overall, AEs led to study drug D/C in 13% of MMB and 6% of RUX pts. In pts with JAKi naive MF, 24 weeks of MMB is non-inferior to RUX for spleen response but not for symptom response. Treatment emergent PN occurred in 22 (10%) of MMB (all Gr ≥3) and 10 (5%) of RUX pts. In previously RUX treated patients, 24 weeks of MMB was not superior to SRR; ≥35% reduction in volume from baseline).

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.

**Results:**

<table>
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<tr>
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<td>T relative rate/month, median</td>
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<td>0.001*</td>
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</tbody>
</table>

*Non-inferiority test; **Superiority test, all values nominally significant.

7003 Deep molecular response to gilteritinib in FLT3-mutative AML patients. 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 (FLT3mut+) 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 an additional time point from FLT3mut+ patients (n=18) 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. A Cox regression model of overall survival (OS) by Kaplan-Meier estimation established a FLT3-ITD threshold for improved survival.

Results: Of 147 FLT3-ITDmut+ patients who received gilteritinib 120 or 200 mg/d, 80 were included in this analysis. Composite response rate for these 80 patients was 55%; complete response, 20% (5/25 patients) had an ITD signal ratio of ≤10-2. Of these 20 patients, 18 had a ratio of ≤10-2 (major molecular response [MMR]) and 13 had a ratio of ≤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 ≤10-2, MMR, or were MRD negative had significantly longer median OS than those who did not.

Conclusions: Molecular responses to gilteritinib in FLT3-ITDmut+ 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.
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 Weill Cornell Medical College, New York, NY

Background: Recurrent mutations in isocitrate dehydrogenase 2 (IDH2) occur in 8-15% of AML pts. IDH2 proteins synthesize an oncometabolite, 2-hydroxyglutarate, causing DNA and histone hypermethylation and blocked myeloid differentiation. Enasidenib (AG-221) is an oral, selective, small-molecule inhibitor of IDH2 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 IDH2-mutated 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 adverse events reported 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 46.3%, including 34 (13.3%) complete responses (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, median 100-day non-relapse mortality (NRM) and 100-day non-relapse mortality (NRM) and 100-day NRM and >100-day NRM were 0%, 2%, and 6%, respectively.

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.

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 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 299 genes (median 280X coverage). We defined 3 levels of mutation clearance (MC) based on variant allele frequency (VAF): MC2, persistent mutation with VAF<2.5%; MC1, persistent mutation with VAF<1%; and complete mutation clearance (CMC). Results: In the pre-treatment samples, we detected 597 mutations in 79 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, MC1, 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 (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 oncosignatures. Pts with deeper MC had significantly better RFS. Somatic mutation clearance may help risk prediction of AML.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 ≥5% blasts as morphologic disease cohort. Response assessment occurred at 4 months. 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 morphologic complete remission (MRD) cohort vs. patients ≥5% blasts as morphologic disease cohort. 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 cohort vs. patients ≥5% blasts as morphologic disease cohort.

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.

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: Tong Hong, Memorial Sloan Kettering Cancer Center, New York, NY

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: Matte D. Hakenberg, 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 allotype-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 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 50 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) against AML and MDS target cells in vitro. To investigate the effect of AT1413 in vivo we first generated mice populated with human effectors (NK cells, T cells, and myeloid cells) by injecting human hematopoietic stem cells into newborn immunodeficient mice. After establishment of a human immune system in these mice, we inoculated subcutaneous xenografts of 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.

Conclusions: AT1413 is a promising antibody-dependent cell-mediated immunotherapeutic agent for AML and MDS. This antibody was able to eliminate AML cells in vivo and therefore has high therapeutic potential.

Additional expression analysis revealed that 42% of a CGAP-curated list of 201 differentially expressed gene clusters, both the MHC class II and interferon-γ responsive gene clusters were enriched with genes involved in the MHC class II and interferon-γ pathways. These results suggest that impairment in the presentation and/or processing of tumor associated antigens by MHC class II or interferon-γ activities could lead to poor response of AML cells to immune response cells and diversion away from LSC by bulk AML, which may contribute to LSC evasion of immune surveillance and response.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 daily) was assessed in pts with CML or Ph+ ALL resistant/intol tolerant 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 as their last dose. In all CP-CML pts (n = 267, efficacy evaluable), cumulative response rates were: MCyR, 60%; CCyR, 54%; MMR, 44%; and MR4.5, 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 clinical program. Clinical trial information: NCT01207440.

Five-year results of the ponatinib phase II PACE trial in heavily pretreated CP-CML (continued).

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) for 4 cycles. Responses were evaluated using standard criteria. Results: As of Oct '16, 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 CR and 1 did not respond. MRD negativity by 6-color flow cytometry was achieved in 31/41 pts (76%) after 1 cycle and in 44/44 pts (99%) overall. Median times to plateau and ANC recovery in cycle 1 were 23 and 16 days, respectively; and 34/42 pts (81%) 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 aleukemic 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-CVD (rituximab + HCVAD + IT chemotherapy) in the University of Texas MD Anderson Cancer Center, Houston, TX, median OS was 142 weeks and 81% of pts received ASCT in CR1. Conclusions: Compared to historical controls, mini-hyper-CVD + INO resulted in higher median OS (54% vs 31%; P = 0.007). A phase 3 study (NCT02129344) is currently accruing; results are awaited. Clinical trial information: NCT01371630.
Effect of cytarabine/anthracycline/crenolanib induction on minimal residual disease (MRD) in newly diagnosed FLT3+ve 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/TP53/DNMT3A/MUT/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 multiple 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/m²/d for 7d and either daunorubicin (≤60: 90 mg/m²); ≤60: 60 mg/m²) or irinotecan 12 mg/m² for 3d. Crenolanib (100 mg tid) was started on day 9 until 72 h prior to next chemotherapy. Results: 29 pts (19M, 14F), median age 64.5y (pts ≥60y are included). MRD at time of count recovery was assessed by MPF in 25/29 pts. 20/25 (80%) became MRD-ve. Age ≥60y was a risk factor for MRD+ve and relapse. All 4 pts with WBC >100K as well as 5 pts with FLT3/TP53/ DNMT3A+ve AML became MRD-ve after one induction cycle and none of the pts 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 FLT3+ve AML. Longer follow-up and comparison of MRA data with similar pts treated with standard chemo alone will be necessary to reach more definitive conclusions. Clinical trial information: NCT02283177.

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 clinicopathologic 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 DAC5-5 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 MDS and AML subsets.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 EFS was 6 months (CI 3.3-11.1 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.

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 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. 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), 295 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 (66% [65/98] vs 60% [108/181], P<.003), and Medicare 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 performed in 9% (15/173) of pts, including 8% (67/99) 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 major part of the registry was underreported. This prospective registry is uniquely positioned to capture changes in testing patterns as guidelines are established.

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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 vs. Cy), and prior lines of treatment. Among sNTX, but we found no association with age, weight, T cell dose, choice of conditioning chemotherapy (Flu/Cy vs. Cy), and prior lines of treatment. Among sNTX cases, IL-5 and IL-2 at day 3 were unique to sNTX. Furthermore, in vivo CAR T expansion and serum cytokines were significantly associated with sNTX (all p < 0.05). The magnitude of these cytokines was especially pronounced in cases IL-5 and IL-2 at day 3 were unique to sNTX. Furthermore, in vivo peak CAR T expansion at day 7 (p = 0.0011) significantly correlated with sNTX (p < 0.01). Lastly, multivariate analysis revealed baseline FLT < 60 or MCHC < 83% 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 cytotoxic 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/m² x 4 doses). Rituximab (if CD20+ blasts) and intrathelial 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) was 9 and 11 months in the S2 and S3 groups respectively. All pts also elevated in serum NTX of any grade. In the S1, 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 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 I/II study of nilotinib with azacitidine (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 (Li Zhang et al, Blood 2009). PD-1 positive DCT C-roles 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 (ECOG = 2), and organ function. AZA 75mg/m² Days 1-7 with nilotinib 3mg/kg on Day 1 and 14 was established at the recommended phase II dose. Courses were repeated every 4-5 weeks indefinitely. Responses were evaluated at the end of courses. Results: 53 pts with med age 68 years (range, 44 – 90), secondary AML (43%), poor risk cytogenetics (43%), and median performance status (PS) = 2). 17 pts (32%) had ≥12% blasts, 79% of these were IPSS Int1 (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 12% pts, respectively. These responses were very durable with 13 pts were successfully rechallenged with nilotinib. 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-treatment 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 nilotinib are generally well-tolerated and may produce durable AML up-regulation of CTLA4 may be a mechanism of resistance to PD1 based therapies. 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: Richard Paul Erba, University of Alabama at Birmingham, Birmingham, AL
Background: The ubiquitous ligand MDM2 inhibits the tumor suppressor p53. In preclinical AML models, MDM2 inhibitors have antitumor activity as mono-therapy 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 in combination 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 (Arm 2). Primary endpoints were MTD, 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 mg (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 were observed; one pt is still on treatment. The MTD was determined as 360 mg based on tolerance of gastrointestinal toxicities. Arm 2 enrollment was at a fixed AMG 232 dose of 210 mg PO QD with or without 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 CR/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. It had favorable biological effects, and early evidence of antileukemia activity. Clinical trial information: NCT0216729.
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 CD19-CAR-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 autologous CD19CAR-T was performed in our clinical trials to induce remission of the low disease free survival even treatment with allogeneic hematopoietic r/r B-ALL was reported as the most-threatening disease because of 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 5 (20%) PRs. 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 (0.689-4.271 months). 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 allogeneic hematopoietic r/r B-ALL with AHA and Methylprednisolone were effective confrontation Severe CRS.

Conclusions: This is the first multicentre report to our knowledge of successful treatment of r/r B-ALL with anti-CD19 CAR T cells in China. Even r/r B-ALL with high-burden leukemia patients also was effective and the 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 Qhanian, 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 in a phase II trial. Hypothesis: Combining sorafenib with AZA (5-azacitidine) is 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/m2 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%) PRs. 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 (0.689-4.271 months). 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 allogeneic hematopoietic r/r B-ALL with AHA and Methylprednisolone were effective confrontation Severe CRS.

Conclusions: This is the first multicentre report to our knowledge of successful treatment of r/r B-ALL with anti-CD19 CAR T cells in China. Even r/r B-ALL with high-burden leukemia patients also was effective and the high remission rate after infused autologous CD19 CAR-T.(NCT 02813837).
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 Hematopoietic 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: AEs were reported as number of pts experiencing events (0-100) vs SOC (0-100) for up to 5 cycles (0-90). AEs were classified as any grade or grade 3/4. The exposure-adjusted (exp-adj) rates (per 100 pts) were calculated as the number of events\(^a\)/total exposure time (Table). Results: Median (range) of cycles were 1 (1-4) for SOC and 2 (1-9) for blin. The highest exp-adj rates (per 100 pts) were for pyrexia (507 SOC vs 376 blin), anemia (987 vs 229), neutropenia (750 vs 126) and Neutropenic events (513 SOC vs 121 blin), 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 3 cytokine release syndrome (CRS) rates were 0 SOC vs 10 blin. The most frequent AEs in both cycles 1 and 2 were pyrexia, rashes 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: This blin showed an AE profile consistent with that previously reported for SOC, including the similar rates of manageable CRS and neurologic events. Exp-adj rates were generally higher in SOC vs blin, including for cytopenias and infections.

Clinical trial information: NCT02031367.

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 analyzed. 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).

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 NPM1 (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, 90% (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 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 hematopoesis 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.

7035 Poster Session (Board #235), Mon, 8:00 AM-11:30 AM

Updated results of frontline ofatumumab-hyper-CVAD in adults with CD20+ acute lymphoblastic leukemia. First Author: Abhishek Maht, 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/PEG-Asparaginase on mos 6 and 18, and O-HCVAD on mos 7 and 19. Interthalactic 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 ± 10³/µL (range: 0.6-201 x10³/µL). 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 overall, and in 36/36 cases on drawing. 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 (40%) and consolidation (35%), and hyperbilirubinemia (21%). 5 pts (7%) experienced a grade 3/4 transfusion reaction. Pts (8%) died in CR1. Pts (16%) have relapsed (morphological, 2 MRD only). Overall survival and 2 year CR duration rates were 86% and 81%, respectively, with no significant independent of percentage of CD20 expression. Conclusions: O-HCVAD is safe, effective and durable in responses in pts with CD20+ ALL. Clinical trial information: NCT01363128.
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. Koltz, 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 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/m2 pts with complete remission (CR) or CR with incomplete platelet or neutrophil recovery). Median OS, mo
Consolidation 2, n/N (%)
24/49 (49) 30/32 (94) 25/49 (51) 2/32 (6)

Conclusions: Some pts can successfully receive CPX-351 consolidation as outpatients without diminished efficacy, potentially reducing hospitalizations associated with treatment administration. Clinical trial information: NCT01966847.

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 debating if autophagy in cancer can lead to therapy resistance or if 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 patients for TP53, FLT3, CEBPA, RUNX1, and NPM1 mutations, and/or CD34- AML status were predictors of response 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 1 17 patients with de novo AML diagnosed between 7/2013 and 12/2014, consecutively treated with HMAs; and 26 received intensive induction. ORRs were 73% and 84%, respectively with HMAs in NPM1 mutated AML are comparable to those of fitter pts and patients 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: IA and FIA have similar efficacy in younger pts with newly diagnosed AML. FIA is associated with a better toxicity profile and may improve outcomes compared to IA in pts <50 years of age. Clinical trial information: NCT01289457.

7039 Poster Session (Board #239), 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: Ghaem C. Issia, 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/m² IV daily on Days 1-3 and cytarabine 1 g/m² IV daily on Days 1-5. Clofarabine and fludarabine were given at 15 mg/m² and 30 mg/m² 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, 16-66) 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 was 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 no more adverse events (all grades) associated with CIA, particularly ASLT adverse events (20% 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 outcomes compared to IA in pts <50 years of age. Clinical trial information: NCT01289457.
NPM1 mut (to all others, pts in cluster 1 had a higher CD34+/CD38- cell burden (monocytic & in cluster 4 (n = 20) of myeloid surface antigens. All 4 clusters in cluster 2 (n = 31) of thrombocytic/T-cell/erythroid, in cluster 3 (n = 24) of substitution. Median follow up was 3.3y. With R median age 63 years [y, range 26-74y] after induction therapy at our in-
received stem cell transplantation (SCT, 98% allogeneic, 2% autologous; common AML gene mutations (mut) & expression levels were analyzed. Pts
nostic implications of surface antigen expression patterns in normal karyotype
Surface antigen expression evaluation is part of the standard
Background:

Unsupervised hierarchical clustering of surface antigen expression to identify
normal karyotype AML patients with distinct disease characteristics and poor
outcome. First Author: Madlen Jentsch, 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 & prog-
nostic implications of surface antigen expression patterns in normal karyotype (NK) AML patients (pts) remain unknown. Methods: The diagnostic antigen expression patterns of monoclonal cells in bone marrow (BM) of 111 NK-AML pts were assessed using a standard flow cytometric protocol. 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 in-
stitution. Methods: 74 patient package units (PPU) were given. The median time from PPU to treatment for about 18 months.

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 in-
duction 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 63-80y). The patient package units (PPU) were given in 4 doses: 1 at 40 mg for 12 days or less; 9 (38%) from 15 to 29 days, 5 (21%) from 33 to 58 days 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 spleenomegaly 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 adverse events were: diarrhea; anorexia; fatigue/weariness; increase ALT/AST, hypokalemia; hy-
potension; febrile neutropenia; dyspnea; 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.
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 transplantation (HCT). A second HCT (HCT2) may be the only possibly curable option; however, it is performed in fewer than 5% of 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 un-manipulated 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 were 26.4%, 14.5%, 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 age ≤ 50 yrs OS (HR 2.0, 95% CI 1.0-3.9) and DFS (HR 2.0, 95% CI 1.0-3.9). 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 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 AEs were necessary before using RIC regimens for HCT2 in patients with relapsed leukemia.

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 younger patients at our center (ST cohort). Methods: Patients in the TS cohort received IV Bu 80 mg/m²/d on days -12 and -13 and IV Flu 40 mg/m²/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/m²/day followed by IV Bu daily for 4 days (day -6 to -3) closed 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 not received a prior unrelated donor allogeneic transplant before 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 CRM status and comorbidity were well balanced and without any significant difference in the two cohorts. Median age was 66 and 65 years in TS and ST 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 notable seen in patients with a comorbidity score ≥ 3. Conclusions: The myeloablative timed sequential Bu regimen improves survival and appears promising in older patients with AML/MDS. Clinical trial information: NCT01572662.
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 pts with T315I. Previously (Mueller ASCO 2016), we reported the positive association of early landmark responses with ponatinib on survival at 3 yr in heavily pretreated pts with CP-CML in PACE (NCT01207440). Here, we provide an update with survival outcomes at 4 yr. Methods: The association of molecular (assessed in a central lab) and cytogenetic responses (CyR) at 3, 6, and 12 mo with 4-yr and 5-yr landmark PFS and OS was evaluated in CP-CML pts (n = 267). P values: calculated using log-rank test. Data cut-off: 3 Oct 2016. Results: At baseline, median time from diagnosis: 7 (range, 0.5–27) yr; median age: 60 (18–94) yr; 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, MCR/CCyR was achieved in 48%/39%/31% and 71%/57%/48% and MMR in 14%/29%/39% of pts, respectively. Greater reductions in BCR-ABL1 transcripts at 6 mo, MCyR/CCyR was achieved in 48%/39%, 62%/52% and 71%/56% and 0.5 (CR) was achieved in 42% (n = 30/71). Select patients up to age 75 progressed with a hypomethylating agent. The groups were well matched into two groups: intensive induction therapy (7+3 based) or induction chemotherapy alone. It is unclear whether IM 400 mg is the optimum choice for the initial therapy of CP-CML. Clinical trial information: NCT00055874. Conclusions: IM 400 mg remains an excellent choice for initial therapy of CP-CML. Clinical trial information: NCT00055874.
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 ≥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% ≥5 yrs, 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.
7059 Postcr Session (Board #259), Mon, 8:00 AM-11:30 AM
Axil blockade in vitro and in patients with high-risk MDS by the small molecule inhibitor BGB324.
First Author: Sonja Logens, Department of Oncology, Hematology, BMT with Section Pneumology and Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Background: The interplay between bone marrow stroma plays an important role in the pathobiology of MDS. Ga63 is secreted by mesenchymal bone marrow stroma cells and promotes survival and therapy resistance of AML cells expressing the Axil receptor. We hypothesized that inhibiting Axil by the small molecule inhibitor BGB324 might hold therapeutic potential in MDS.

Methods: We investigated the inhibitory effect of BGB324 on primary bone marrow stromal 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 stromal cells (BMMNC) and mesenchymal stromal cells (MSC) from MDS patients in comparison to healthy donors. In the ongoing first-in-patient Phase 1b trial (NCT02211713; [ClinicalTrials.gov Identifier: NCT02211713]; [ClinicalTrials.gov Identifier: NCT02211713]) in patients with high-risk MDS, BGB324 was administered as an oral loading dose on days one and two followed by a reduced daily maintenance dose. 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, BMMNC from healthy donors were resistant to BGB324 (IC50 9.4 μM, p < 0.05, n = 10). Axil 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 (HR = 2.5 μM and 2.7 μM, respectively, p < 0.05). To further demonstrate the potential of BGB324 in MDS, 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. 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 phosphorylated Erk and phosphorylated Akt signaling at day 21 of treatment. Conclusions: BGB324 was well tolerated and may represent a promising novel treatment approach in MDS. Safety and efficacy of BGB324 will be explored further in clinical trials. Clinical trial information: NCT02488408.
Background: Our objective was to evaluate whether the addition of interphase FISH analysis to standard chromosome analysis (CA) improves the detection of myelodysplastic syndromes (MDS), acute myeloid leukemia, and myelodysplasia/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/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 stand-alone 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 cases (N = 247, 23.17%) as compared to standalone FISH analysis limited additional utility in cases with a complete CA. Findings suggest that FISH studies with 4 markers used in this study provides diagnostic and prognostic value of FISH in addition to CA for patients with MDS, acute myeloid leukemia, and myelodysplasia/myeloproliferative disorders.

Conclusions: These findings suggest that FISH studies with 4 markers used in this study provide diagnostic and prognostic value of FISH in addition to CA for patients with MDS, acute myeloid leukemia, and myelodysplasia/myeloproliferative disorders.
Ruxolitinib (RUX) in combination with azacitidine (AZA) in patients (pts) with myelodysplastic/myeloproliferative neoplasms (MDS/MPN). First Author: Risa 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 platelet count) orally twice daily continuously in 28-day cycles for the first 3 cycles. AZA 25 mg/m² (day 1-3) was added on each cycle starting cycle 4 and could be increased to 75 mg/m² (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; CMMML, n = 17; atypical CM (aCMPL), n = 4), 28 (80%) were Int-2/High per MF DiPSS, 14 (41%) had splenomegaly > 5 cm, and 12 (34%) had EUNMFT-M2/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 prior cryoablation 8M 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 aCMPL, MDS/MPN-U pts had significantly better survival (26.4+ vs 15.0+ vs 15.0+ 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).
Background: Gilteritinib, a highly selective, potent FLT3/AXL inhibitor, was designed to target CD123-positive cells for recognition and elimination by the immune system. CD123, the alpha chain of the interleukin 3 receptor (IL-3Ra) is known to be highly expressed in 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: SY-1425 is currently being evaluated in a Phase 1 dose-escalation and cohort expansion study in 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 RARA pathway biomarker, IRF8. SY-1425 also induces the RARα (retinoic acid receptor alpha) and predicts for response to SY-1425 with induced differentiation and 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 patient xenograft models. SY-1425 also induces the RARx target gene DHR32 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 >60 yrs unlikely to respond to or tolerate standard therapy, and transfusion dependent lower-risk MDS pts without del5q 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/m²/day PO with continuous twice daily dosing. Primary objectives are to characterize the activity of SY-1425 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 DHR32 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: NCT02993523.

TPS7070 Poster Session (Board #268a), 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 (tamborotene) 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 RARA pathway biomarker, IRF8. SY-1425 also induces the RARα (retinoic acid receptor alpha) and predicts for response to SY-1425 with induced differentiation and 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 patient xenograft models. SY-1425 also induces the RARx target gene DHR32 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 >60 yrs unlikely to respond to or tolerate standard therapy, and transfusion dependent lower-risk MDS pts without del5q who are unlikely to respond to or have failed ESAs. Pts must be biomarker positive based on central testing of tumor cells from blood. All pts receive SY-1425 at 6 mg/m²/day PO with continuous twice daily dosing. Primary objectives are to characterize the activity of SY-1425 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 DHR32 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: NCT02993523.

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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 the BR and R-CHOP/R-CVP. Similar results were found in iNHL (PFS 0.70 vs 0.61; P = .0582) and MCL (PFS 0.40 (0.21-0.75; P = .0053), 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.

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 well balanced 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. The extended PFS rate for PFS was improved in non-del(11q) pts within each arm. A total of 147 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. The extended PFS rate for PFS was improved in non-del(11q) pts within each arm. A total of 147 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. The extended PFS rate for PFS was improved in non-del(11q) pts within each arm. A total of 147 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%.
7504 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Ublintiximab and ibritinib for previously treated genetically high-risk chronic lymphocytic leukemia: Results of the GENUINE phase 3 study. First Author: Jeff Porter Sharman, Williamette 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 ibritinib (IB) mono-

therapy (O’Brien AH 2016). Ublintiximab (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 ibritinib in high-risk rel/ref CLL, and evaluates IB monotherapy vs. UTX + IB.

Methods: Eligible pts with rel/ref CLL and centrally confirmed del(17p), del(11q), and/or a TP53 mutation randomized 1:1 to receive IB (420 mg Q2W) alone or with UTX (900 mg on D1, B, 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% were male. High-risk cytogenetics were relatively balanced with ~50% of pts having del(17p). UT+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 GR<3/4 AEs were lower with UTX + IB, 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: UTX + 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 IGIV unmutated, VH1-69 10/43 (23%), VH4-39/4- 43% (9%). 59 (83%) pts were treated as 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 (32%), 70-90 (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 (4%). RS were 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 2.6-6.0), 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. The addition of UTX to CR is of interest. Further development of novel treatment strategies are urgently needed.

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Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia

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 chemoinmunotherapy 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 chemoinmunotherapy) 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 chemoinmunotherapies 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 (AP) of NRM were significantly lower with autoHCT (5%), versus MSD (17%) or MUD (33%) HCT (p<0.0001). The 5 yr AP of relapse were significantly lower with MSD (31%) or MUD HCT (23%), versus autoHCT (38%; p<0.0001). AP of 5 yr OS following auto, MSD, and MUD HCT were 38%, 52% and 43% (p=0.006) respectively. The AP of 5 yr OS was significantly higher following autoHCT (70%) or MSD HCT (73%) versus MUD HCT (49%; p=0.0004). 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.

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 when 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 concomitant 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. 1 pt developed gr4 lysis syndrome. Treatment of CRS with the IL-6 receptor antagonist tocilizumab was not required. At 3 months, 8 evaluable pts had 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 aneuploidy resolved in 4/5 subjects with progression in 1/5. 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.

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 PI3K/mTOR 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 + PI3K/mTOR inhibitor (ibrutinib) in pts with B-cell malignancies. Methods: Eligible pts had CLL or rel/ref NHL w/o limited to prior therapies, including those ref to prior PI3K and BTK inhibitors. UTX dosed on D1, D15 of C1-C2, and C2 of 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-ys (range 32-86), 29 M/F, med prior tr = 3 (range 0-6). 2 pts were ref to prior PI3K 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 (26%), neutropenia, pancytopenia, 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 among 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 at 400mg of TGR-1202 plus 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 triplet combination of an anti-CD20 mAb + PI3K/mTOR 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.

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Clinical and biological covariates of outcomes in ZUMA-1: A pivotal trial of axicabtagene ciloleucel (axi-ctl; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (r-NHL). First Author: Frederick Locke, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Outcomes in activated B cell subtype diffuse large B cell lymphoma (ABC-DLBCL) and n-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, and the only CAR trial investigating Ibrutinib in patients with r/r PCNSL and SCNSL.

Methods: Eligible patients had r/r PCNSL or SCNSL, age ≥18 years old with R-R DLBCL, ECOG 0-1. 31 of 80 planned pts were enrolled prior to data cutoff (3 January 2017). Median age was 74 years (range 47–98) 64% had PCNSL and 36% SCNSL; 68% had Ann Arbor stage IV, 65% had elevated lactate dehydrogenase (LDH) and 65% had a history of treatment with at least two prior therapies. 80 patients were treated with Ibrutinib and MOR208 (12 mg/kg IV, weekly during C1 – 21, C1 – 21, C1 – 21). Every second week 1.2 + 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 planned 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 47–85); 78% pts 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 1.2 + 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 planned safety evaluation was undertaken.

Conclusions: The combination of MOR208 + LEN is well tolerated and shows promising activity in pts with R-DLBCL. Accrual and follow-up of pts is ongoing, as are cell of origin and other biomarker analyses.

Clinical trial information: NCT02348216.
Phase I clinical trial on pamidronide 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. Pamidronide (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 in combination with dexamethasone 40 mg PO weekly for 2 cycles followed by POM alone in subsequent cycles until progression or intolerance. 4 dose escalation levels of POM (3 mg, 5 mg, 7 mg, and 10 mg) were planned. Thrombophrophilaxis 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.

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 lymphopenia). ORR for the study (N=21) was 43% (95% CI:22-79). 66% with CD1, CRs 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). Progression of disease 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 maculopapular rash). Percent CSF/pleural ratio of POM was determined to be 19% in 1 patient.

Conclusions: Pamidronide treatment is feasible with therapeutic activity against relapsed/refractory PCNSL and should be further developed. Clinical trial information: NCT01722305.

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Background: Both ibr and ven have activity in relapsed/refractory (R/R) MCL, but effectiveness and toxicologic profile of the combination have not been determined. The objective of this study was to evaluate the safety, activity, and tolerability of the combination of iFCG (ibrutinib + bendamustine + GA101) in patients with R/R MCL.

Methods: Eligibility included age ≥18 years, histologically confirmed MCL relapsed/refractory or intolerance to previous therapy who did not respond to the last therapy given. Patients started iFCG at the following dosing schedule: ibrutinib 420mg once daily, bendamustine 280mg/m2 on days 1-5, 8-11, and 14-17 every 28 days, and GA101 1000mg on days 1, 8, 15, and 22 every 28 days. The primary endpoint was CR rate assessed using iwCLL criteria on best response. Secondary objectives were PFS and OS.

Results: 20 patients were enrolled and 18 were evaluable for safety and efficacy (1 pt. withdrew consent). Grade 3-4 adverse events included lymphopenia (21%), neutropenia (20%), and anemia (17%). The most common Grade 3-4 events were fatigue (11%), diarrhea (11%), nausea (11%), and infection (9%). 7 patients (39%) were MRD negative (MRD-). Median time to MRD- was 5.7 (IQR 2.0-11.1) months. 1 pt was MRD+ at 1 year continuing to receive treatment. Median time on therapy was 8.7 (IQR 3.8-13.0) months. Of the 18 evaluable patients, 15 (83%) achieved MRD-negative response (MRD-) in blood, as measured by qPCR for BCR-ABL1 (3.14E-12 copies/mL), and 11 of 15 patients (73%) achieved MRD-negative response in BM, as measured by qPCR for BCR-ABL1 (1.39E-15 copies/mL).

Conclusions: The regimen of iFCG is feasible with limited toxicity, and achieves high rates of MRD-neg remission in blood and BM after 3-6 cycles. Moreover, 11 patients completed 3 cycles of iFCG and had initial response assessment (the on-treatment cohort). Our results compare favorably with historical results, and warrant further phase III investigation.

Clinical trial information: NCT02471391.

Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia

7520 Poster Discussion Session; Displayed in Poster Discussion 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: Enrollment 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 toxicity (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^-2 to 10^-3). Using CT without PET, the comparison responses were CR 42%, CRu 17%, PR 17% (ORR 78%).

Discussion: Both ibr and ven have activity in R/R MCL, but their efficacy and tolerability profile when combined is not well understood. A dose-escalation portion of this study is ongoing to determine the optimal dose of ven.

N=18 Marrow MRD N=18 Marrow MRD

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7521 Poster Discussion 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, Cancer Center, 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, 85 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 databases. 0.4 months (95% CI: 0.29-0.61). This difference held up for each of the major histologic subsets, including PTCL-NOS 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: NCT03864923.

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Ibrutinib vs chlorambucil: Immunophenotypic and quantitative impacts on circulating immune cells in chronic lymphocytic leukemia (CLL).

**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: Ibr 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 (TSCM), decreased by 51%-90%. Long-term activated T cells (T-A) were also decreased (61%-69%). On the other hand, ibr mainly reduced B cells (90%), MDSC (61%) and some T cells, specifically T-NK, PD-1+ T cells, Treg and effector T cells (27%-52%). Naïve T cells, TNA, central memory T cells and NK cells were spared. Classical monocytes were increased (+187%), while non-classical monocytes and intermediate monocytes remained relatively stable. Conclusions: Chl, a traditional chemotherapy, affected non-specifically most immune cell subsets in circulation, although surprisingly it did not affect T-A, 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, Treg, PD-1+ T, Treg, and pro-tumor MDSCs were reduced. However, ibr preserved naïve T cells, NKT cells and monocytes, which are important for mounting anti-tumor responses. Clinical trial information: NCT01722487.

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, SLVCA 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 provide definitive and effective disease control 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 treated at the VA were identified from the VA-Clinical Data 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 (42%). Median age was 73 years, 71% male, 75% white, 12% with del17. 26% of pts were older than 75 years of age, and 76% were frail/older as per ECOG criteria. **Conclusions:** Cytogenetic/FISH testing is widely used in patient care. As novel regimens are introduced and become more prevalent, we project a significant increase in cytogenetic testing to guide treatment options and decision making.
Background: Classical Hodgkin Lymphoma (cHL) is one of the diseases in which the check-point inhibitors have been demonstrated to be more successful. Laterly, 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 has already failed. Unfortunately, the detection of the genetic alterations in RSCs is challenging, as one of the hallmarks 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 polyclonal 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 (AmpTi™ WGA), and genome-wide copy-number aberrations (CNAs) profiles were obtained using AmpTi™ 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 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 abundant 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.

N° OR, n (%) CR, n PR, n

All pts 45 22 (49) 10 12
NHL 31 19 (61) 10 9
DLBCL 14 5 (36) 3 2
MZL 7 (78) 2 1
MZ 4 (100) 2 2
MCL 4* (75) 3 0
CLL 2* (33) 0 1
HL 8 1 (13) 0 1

* Evaluable pts. 1 Radiologic/metric.

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 Ramchandani, Karmanos Cancer Institute, Detroit, MI

Background: INCB050465 is a selective PI3K6 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. 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 large expanded. Responses were assessed q2w 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 56 y, range 30-88), baseline tumors: diffuse large B-cell lymphoma (DLBCL) n=11, follicular lymphoma (FL) n=10; Hodgkin lymphoma (HL) n=9; marginal zone lymphoma (MZL) n=8; CLL n=6; mantle cell lymphoma (MCL) n=6; 62% had ≥3 prior regimens. Median therapy duration 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% reduction. Most common nonhematologic AEs (all grade; Gr): diarrhea (50%; Gr 3: 6%); 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 jiroveci pneumonia (PiP) 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 transaminas/PiP. 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.

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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 (Coiffer, ASH 2016).
Methods: A total of 140 patients were randomized in a 1:1 ratio to receive CT-P10 or RTX (375 mg/m² 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: Non-inferiority 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 -4.2%. B-cell depletion 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 any group. Conclusions: This study demonstrated non-inferiority of efficacy of CT-P10 to RTX combined with CVP in previously untreated AFL. CT-P10 was well-tolerated and the safety profile demonstrated non-inferiority of efficacy of CT-P10 to RTX combined with CVP in patients with newly diagnosed advanced follicular lymphoma (AFL) (NCT02162771).

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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-PI3K (PI3K) inhibitor, with modest single-agent activity in unsellected 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).

Results: The primary endpoint was objective tumor response rate (ORR; per Lugano Classification, 2014) by COO and CD79B status.

Conclusions: Copanlisib demonstrated modest single-agent activity in r/r DLBCL patients with a manageable toxicity. Clinical trial information: NCT02391116.

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 patterns associated with the COO.

Methods: Here, we further explore the mutational patterns in patients with differing molecular subtypes of DLBCL based on sequencing of circulating tumor DNA.

Results: We applied cancer personalized profiling by deep sequencing (CAPP-Seq) to pretreatment plasma samples and matched germline DNA. The median age 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 (40/3) and hyperglycemia (34/3). There were 14 gr3 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.

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 naive pts with FL with an injectable tumor site and distal sites of disease were eligible. In Part 1, G100 cohorts of 5 or 10 μg were enrolled in a 3+3 design, followed by a larger 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 21st 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.

Conclusions: 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 (4 responding at 15 cycles), 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.

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 G100 and 4 applications of rituximab. Anti-infective prophylaxis consisted of ciprofloxazine (500 mg/d) during days of severe 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.

Conclusions: Anti-infective prophylaxis with aciclovir and cotrimoxazole is associated with reduced 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.
**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 of 40 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 (5/40), B symptom (40%), elevated serum LDH (40/40), regional lymph node involvement (32/50) 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%, 87.2%, 79.7%, respectively. Recurrence within the RT field was observed in 21 patients and systemic failure in three individuals. Grade 2-3 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 seen in 41% (16/39) of patients and 3% (1/39) had late neurotoxicity and 12% (4/39) of patients. **Conclusions:** 2-year OS was 59.3% and 57.3% in MYC- and MYC+ patients, respectively. The median OS was 120 months (95% CI 72.4-167.6) and the rate of disease recurrences was 10% (95% CI 4.5-20.2). The 2-year rate of venous thromboembolism (VTE) was 2%. No secondary malignancies were observed (2/40). With the use of this regimen, we observed 4% grade 2-3 skin reactions and mucositis were the main toxicity related to radiation. Grade 2-3 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 seen in 41% (16/39) of patients and 3% (1/39) had late neurotoxicity and 12% (4/39) of patients. **Conclusions:** 2-year OS was 59.3% and 57.3% in MYC- and MYC+ patients, respectively. The median OS was 120 months (95% CI 72.4-167.6) and the rate of disease recurrences was 10% (95% CI 4.5-20.2). The 2-year rate of venous thromboembolism (VTE) was 2%. No secondary malignancies were observed (2/40). With the use of this regimen, we observed 4% grade 2-3 skin reactions and mucositis were the main toxicity related to radiation. Grade 2-3 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 seen in 41% (16/39) of patients and 3% (1/39) had late neurotoxicity and 12% (4/39) of patients.
Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia

7544 Poster Session (Board #306), Mon, 8:00 AM-11:30 AM
Phase I dose escalation of ibritrubin and buparlisib in relapsed/refractory diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL). First Author: Connie Lee Battey, 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 Ib/II investigator-initiated clinical trial evaluating the combination of ibritrubin (BTK inhibitor) and buparlisib (pan-PI3K inhibitor) in relapsed/refractory (R/R) NHL. The completed dose escalation was reported. Methods: Patients (pts) were eligible if they had R/R DLBCL, MCL, or FL with ECOG ≤ 2 and adequate organ function. Ibritrubin 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 is 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 of any grade ≥ 20% across all pts were fatigue (77%), diarrhea (62%), anorexia (54%), rash (46%), hyperuricemia (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 3 pulmonary embolus (N = 1), grade 1 fever with hospitalization (N = 1), grade 2 confusion and grade 4 hypotension (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 5). One CR was a MCL Pt with CR after 2 cycles on combination therapy and continues in remission on ibritrubin alone because of buparlisib toxicity. Conclusions: Combination of ibritrubin and buparlisib while generally well tolerated has predicted toxicities of both BTK and PI3K inhibitors. The recommended phase 2 dose is ibritrubin 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.

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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 IC50 against SYK and JAK; decreases proliferation in ibritrubin-resistant cell lines, and suppresses tumor growth in rodent xenograft models of NHL and other hematologic malignancies. Methods: This Phase I/II clinical trial in patients with solid tumors and hematologic malignancies evaluates escalating ASN002 oral doses of 10, 20, 30, 40, 50 and 75 mg ID 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 ID 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 (Cmax, AUC (0-12h) and T1/2 at 40 mg ID were 0.7 μM, 6.3 μM·h and 18, respectively). High systemic exposure was also observed at 80 mg QD. Robust reduction of CRP, IL-18, MIP1β, VACM-1, TNFR2 was observed at all doses. Stable disease (RECIST, ≥ 9 months) in a patient with primary central nervous system disease, 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.

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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 (ys) 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 IIIE) 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 (sIL-2R level > upper limit of normal (ULN) (25/33, 76%; P = 0.0000012), 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.

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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/ Rituxan (R2CHOP) vs RCHOP in ABC-DLCL 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 interval rate (IR), the protocol was amended to include time points 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, for a submitted tissue block of 4 μM, and CD30, CD15 and CD20 were used to ensure that 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 appropriate 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 2.9 WD (0.033). 90% were negative predictive value of elevated sIL-2R for 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.

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375 mg/m² + CHOP. Primary objective was to compare C1 PK (AUC 0-21d & Cmax) in C1, within 80-125%.

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 9.3 months, p = 0.05), but difference in OS did not reach statistical significance (29.5 vs 22.4 vs 16.6 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.

Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia

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: Natallie 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 9.3 months, p = 0.05), but difference in OS did not reach statistical significance (29.5 vs 22.4 vs 16.6 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
Oncocogenic activation of STAT3 pathway drives PD-L1 expression in natural killer/T cell lymphoma. First Author: Soo Thye Lim, National Cancer Centre Singapore, Singapore, 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 compared to Western Europe and the USA, 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. BaF3 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 kinase domains. A characteristic of novel mutations was that all were located on the C terminus of the protein. There was no significant difference in OS between patients harboring STAT3 mutations and patients without mutations (88.9 months vs 106 months, p = 0.73). Conclusions: p-STAT3 expression was observed in tumor tissue (R = 0.51, P = 0.02). 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. Further studies are needed to validate this approach in NKTL.
Circulating tumor DNA assessment in patients with diffuse large B-cell lymphoma following CAR-T therapy. First Author: Saurabh Dahya, Stanford University School of Medicine, Stanford, CA

Background: Circulating tumor DNA (ctDNA) has been used for disease monitoring in Diffuse Large B Cell Lymphoma (DLBCL) (Kurtz ASCO 2016). Role of ctDNA assessment in DLBCL patients treated with CAR-T therapy has not been studied. We prospectively analyzed ctDNA of dynamics measured by next generation sequencing (NGS) of BCR using ClonoSeq MDR (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 ctDNA analysis was collected for six subjects. Tumor DNA was extracted from archival paraffin-embedded 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 ctDNA by ClonoSeq quantification of clonotypes.

Results: Clonotypes were successfully determined for all six subjects, and 30 blood samples for 6 patients were prospectively analyzed. All patients had measurable disease burden pre-CAR-T infusion. ctDNA dynamics correlated with PET-CT outcomes in 100% of the patients. Increasing ctDNA temporally preceded progressive disease (PD) before PETCT recognition in 4 of 5 patients and was always increasing when PETCT showed PD. Preceding ctDNA quantitation was uncorrelated with disease volume increase. One patient achieved durable KTE-19 complete response (CR) and detectable ctDNA 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 ctDNA in the B-cell setting. This technology may overcome limitations of DLBCL imaging (cost, radiation exposure & limited repetition).

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occurred in our patient population. Two patient deaths were attributable to aGVHD, and CI: 1.05-7.34, p = 0.04). Low rates of grade III/IV aGVHD (n = 4) and relapse (n = 4) received more than 3 lines of prior treatment had a higher risk of death (HR: 2.77, 95% of patients (n = 23, 79%) had 3 or more lines of treatment prior to allo-SCT. The 5 year – for MCL needs further clarification. Our data supports early opposed to delayed allo-

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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 analysis. We identified 16 cases of HGBLR (3%), 26 cases of HGBL, NOS and 765 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). At a median (range) follow up of 4(1-155) months, median PFS and OS for DLBCL was not reached. For HGBLR vs HGBL, HGBL NOS patients 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 HGBL NOS vs DLBCL was 2.9 (1.32-5.07), p = 0.01 and 1 1.80(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 HGBLR 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 HGBLR-R and HGBL, NOS patients in our series.
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 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, >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 ≥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-treatment biopsies showed reduction of the PI3K/AKT, JAK/STAT, and NFκB 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 >35% 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 entoceptinib (ENTO) in patients with lymphoplasmacytoid lymphoma/Waldenstrom's macroglubulinemia (LPL/WL). First Author: Sanit 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 kinase of B-cell receptor (BCR) signaling. Targeting the BCR-signaling pathway has been a focus in B-cell related hematological malignancies including LPL/WL. 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 (71%), 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/≥grade 3, independent of causality) were fatigue (53%, 6%), constipation (47%, 0%), nausea (47%, 6%), diarrhea (29%, 6%), infection (29%, 0%) and anemia (12%, 0%). Overall response (ORR) was 82% (95% CI: 44%, 95%), median duration of response has not been reached. Conclusions: ENTO was well tolerated and demonstrated limited activity in patients with R/R LPL. Further exploration of ENTO in LPL will focus on its role in combination therapies. Clinical trial information: NCT01799889.

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A phase I trial of CD19-targeted EGFR1/19-28z/4-1BL CAR T cells in patients with relapsed or refractory chronic lymphocytic leukemia.

Background: Despite the recent progress in the therapy of CLL with BTK, PI3K, 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 second 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 is due to the inhibitory tumor microenvironment (TME) of CLL. We believe one approach to over the hostile TME is through the use of CD19-CAR T cells further modified to express a second costimulatory ligand, 4-1BL. A binding of 4-1BL 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 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 EGFR1/19-28z/4-1BL* 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 (EGFR). 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 - 3x10^7 CAR T cells/kg). The primary endpoint is safety and maximum tolerated doses of the CAR T cells. 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.

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-) 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-RR-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 plus BEN in patients with R-RR-DLBCL. Methods: B-MIND is a randomized (1:1), two-arm, multicenter, open-label, adaptive design, phase II/III study of MOR208 plus BEN vs RTX plus 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 line of therapy 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: prior 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 Lundy Locke, H. Lee Moffitt Cancer Center 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 (Cheston 2007). Secondary endpoints include key efficacy outcomes such as objective response rate (OR=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 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/m²/day and cyclophosphamide 500 mg/m² d/3, followed by a single infusion of axi-cel (target dose, 2 × 10^9/kg) on days 1-14. Both arms receive atezolizumab 1200 mg given every 21 d for 4 doses (phase 1, first dose to occur on 21, 14, and 28 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 to evade immune cell detection and inhibit antitumor responses. PD-L1/PD-L1 expression in multiple hematologic malignancies may provide an effective target for enhancing antitumor and immunotherapy. 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 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 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 2015-001573-20; NCT03030520). High risk was defined as Ann Arbor stage III/IV or II with bulky disease (≥7.0 cm), along with intermediate-high/high IPI; NCCN-IPI ≥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) and Arm B (ABC) receive 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 days 1 and 28 for 8 months from induction cycle 1, day 1. The primary endpoint is 2-year 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: NCT03030520.

TPS7574 Poster Session (Board #332a), Mon, 8:00 AM-11:30 AM
Phase 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-L1/PD-L1 expression in multiple hematologic malignancies may provide an effective target for enhancing antitumor and immunotherapy. 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 with R-CHOP in non-activated B-cell-like (non-ABC) and 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 ≥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 asbocap 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 mWCL 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 I/II 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 rituximab (a monoclonal anti-CD20 Ab), and/or additional pts randomized 1:1 to the chosen regimen or investigator’s choice CT (rituximab/bendamustine or rituximab/gemcitabine/oxaliplatin). The primary phase I/II 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 Ib will be selected for phase 3 evaluation in 220 additional pts randomized 1:1:1 to the chosen regimen or investigator’s choice CT (rituximab/bendamustine or rituximab/gemcitabine/oxaliplatin). The primary phase III 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/multimodal CT, and/or failed autologous hematopoietic stem cell transplantation (ASCT), or are not eligible for intensive CT or ASCT. Other eligibility criteria include ECOG PS ≤1 and no prior therapy with a checkpoint inhibitor. Treatment with avelumab, rituximab, 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 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.
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 (PERSEPTIVE).

**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-naive (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, frontline treatment with ibrutinib in combination with rituximab results in prolonged PFS compared to rituximab alone, and (2) whether continuous versus finite treatment with ibrutinib affects PFS outcomes. **Methods:** In the ongoing PERSEPTIVE trial, approximately 440 patients with TN FL meeting at least one Group 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. Key exclusion criteria include any prior treatment for FL, evidence of CNS involvement, or transformation. Analyses will be conducted in two parts and will uniquely test (1) whether frontline treatment with ibrutinib in combination with rituximab results in progression of PFS compared to rituximab alone, and (2) whether continuous versus finite treatment with ibrutinib affects PFS outcomes.

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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/m² on C1D1, 36 or 70 mg/m² 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/m² 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 to 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.

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 treatment with elo plus len 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 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 73% (18/24). 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 sepsis 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 high-grade toxicities was low, although there were two grade 5 events (sepsis 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 III studies showed the safety and efficacy of KRd and KCd in NDMM pts (Jakubowiak Blood 2012, Brusinhen 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/m² IV d 1,2,8,9,15; cyclophosphamide:300 mg/m² d 1,8,15) followed by MEL200-ASCT and 4 KRd 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 mg/m², followed by PBSC collection. We report the 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 (KRd, n=94; KCd, n=187). The most frequent grade 3-4 AEs plus SAEs in both arms were hematological (mainly neutropenia and infections) and cardio pulmonary (increase in AST/ALT/GGT (mainly reversible) and dermatological (rash)) AEs. 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, 95% vs 95% (P=0.44) of pts mobilized stem cells (median number of PBSC collected 9 vs 6x10^6 CD34/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. Clinical trial information: NCT02203643.
RRM2b or bortezomib plus dexamethasone (DVD) in relapsed or refractory multiple myeloma (RRMM) based on cytogenetic risk status. First Author: Katja C. Wiesel, Universitaetsklinikum Tuebingen der Eberhard-Karls-Universitaet, Abteilung fuer Innere Medizin II, Tuebingen, Germany

Methods: The MTD of weekly K in the KMP combination is the maximum tolerated dose (MTD) of K weekly. 4 cohorts of 6 patients each were recruited at 70 mg/m², with increased attention around hyperkalemia (grade 2/3) and severe hyperkalemia (grade 4) in the setting of AKI. The recommended dose was 60 mg/m² every 2 weeks for 1 year. 3 dose-limiting adverse events (DLTs) defined MTD at the lower N1 dose. Results: 27 patients were included. Median age was 75 years, 56% patients were R-ISS 2 or 3. The overall response rate was 87% including 67% very good partial responses and 44% complete responses. Conclusions: The MTD of K is 60 mg/m² every 2 weeks in patients with baseline creatinine clearance (CrCl) > 60 mL/min. DMB was non-inferior to ZA (P = 0.01) in delaying 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 < 60 mL/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 AE 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 > 60 mL/min (8.8% vs 14.2%) and particularly in those with baseline CrCl = 60 mL/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 (6.29, 24.82) for ZA. PFS was not different in both arms. DMB is effective in pts with baseline renal insufficiency (CrCl < 60 mL/min). The bone specific benefits in combination with the renal function results and possible prolongation of PFS will allow KMP's approval of dexamethasone in Europe. Females made up 41.0% of the study population, and 67 pts had a history of previous treatment with dexamethasone. DMB therapy is promising. Clinical trial information: NCT01345019.
Clinical trial information: NCT01109004. TAM predicts for longer PFS and OS is the subject of ongoing analysis. Whether accomplishment of CR/minimal residual disease after AM, ACM, or not associated with PFS or OS. High-risk had an adverse association (95% CI: 1.01-2.26). adverse association for PFS (HR 1.62, 95% CI: 1.27-2.07) and OS (HR 1.51, 95% CI: 0.96, 2.35).

Analyzing response, risk category, and Rx revealed no 57.1% (46.8%, 66.1%); ACM: 60.1% (50.1%, 68.7%); AM: 55.1% (45.1%, 64.0%). Kaplan Meier estimates of FFS and OS were performed as a function of Rx and very good partial response (VGPR including CRs) vs. < VGPR. Cox proportional hazard models explored associations between FFS or OS and risk category, Rx, and vs. VGP. Results: Between 6/2010-11/2013, 758 pts (AM, N = 257; ACM, N = 254; TAM, N = 247) aged 20-70 years old were randomized to melphalan 200mg/m^2 (mel) and AHCT (AM), tandem AHCT and len maintenance (TAM) for up-front treatment of patients (pts) with multiple myeloma (MM): BMM CTN0702-stamina (NCT01109004). First Author: George Somlo, City of Hope, Duarte, CA. Background: The Stamina trial primarily aimed to identify the best strategy overall survival (OS) and baseline MM response, risk category, and treatment (Rx). Grade 3-4 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 BP regimen is relatively tolerable and achieves a promising overall response rate (ORR of 72%) and durable responses in a heavily pre-treated lenalidomide population with prior bortezomib exposure, and a median of 5 lines of prior therapy. Clinical trial information: NCT01754402.

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, and dexamethasone) and in maintenance (AM vs. ACM) versus tandem AHCT and len maintenance (TAM) for up-front treatment of patients (pts) with multiple myeloma (MM): BMM CTN0702-stamina (NCT01109004). First Author: George Somlo, City of Hope, Duarte, CA. Background: The Stamina trial primarily aimed to identify the best strategy overall survival (OS) and baseline MM response, risk category, and treatment (Rx). Grade 3-4 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 BP regimen is relatively tolerable and achieves a promising overall response rate (ORR of 72%) and durable responses in a heavily pre-treated lenalidomide 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. Johnson, 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 33.6 months, 965 DFS 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 55%. This was associated with a significantly improved median PFS (HR 0.85, 95% CI: 0.72-0.97, p = 0.02), median OS (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 0.42, 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= 50.2%, CTD= 39.1%, CRD= 18.0%, CTD= 23.4%. Conclusions: CRD was associated with CRD 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: NCT01545852.

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) or Bortezomib-Lenalidomide-Dexamethasone (VRD) vs no consolidation, and intensification 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^-6. Quality checks were performed to compare sensitivity and to show correlation between protocols (Hofste gubruinik 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 del17q, t(4;14) or (14;16), 63% (199/316) had received HDM and 37% (117/316) VMP, thereafter 51% (160/316) had received VRD. 76% (233/316) had NL (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 serum M-protein 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.
Bendamustine with ixazomib and dexamethasone (BID) for double refractory relapsed multiple myeloma (RRMM): Phase I safety and dosing results. First Author: Biuczak, 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, and 3 of each cycle with weekly ixazomib (4mg) and dexamethasone (40 mg) on days 1, 8, 15 and 21 for up to 8 cycles in responders and 4 cycles for 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%), diaphoresis (7%), anemia (7%), lung infection (7%), and skin ulceration (7%). Three (20%) pts. died of myeloma progression. In dose cohort 3 (bendamustine 90 mg/m^2), 2/6 pts. developed hematologic DLTs (neutropenia and thrombocytopenia meeting MTD; RP2D was determined to be 80 mg/m^2). 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.

<table>
<thead>
<tr>
<th>BID arm</th>
<th>N</th>
<th>Evaluable pts</th>
<th>Response</th>
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<tbody>
<tr>
<td>70mg/m2</td>
<td>3</td>
<td>1</td>
<td>SD, PRD</td>
</tr>
<tr>
<td>80mg/m2</td>
<td>6</td>
<td>2</td>
<td>VGPR, 2PR, 1PD</td>
</tr>
<tr>
<td>90mg/m2</td>
<td>5</td>
<td>1</td>
<td>PR, CR, PRD</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>11</td>
<td>ORR-45% (3/1), CBR-73% (6/1)</td>
</tr>
</tbody>
</table>

SD = stable disease; VGPR = very good partial response; PR = partial response; PD = Progressive disease. Response in 3 cohorts.

**Conclusions:** BID was an acceptable safety profile and a promising ORR of 45% and CBR of 73% in pts. with advanced disease. In PhII (4mg Ixz) portion of the trial, ORR and CBR were 54% (9/17) and 82% (14/17) respectively for pts. refractory to a proteasome inhibitor -containing combination regimen. 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 MTD was not determined, then patients were enrolled in an ascending dose cohort of Ixz.

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WT1 heteroclitic epitope immunization following autologous stem cell transplantation in patients with high-risk multiple myeloma (MM). First Author: Guanther Koehe, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Host T-cells mount immune responses (IR) against Wilms tumor 1 (WT1) in A*0201+MM pts through formation of WT1 peptide. WT1 heteroclitic epitope immunization following autologous stem cell transplantation (SCT) and 122A1-L: SGQAY*MFPNAPYLPSCLES. 2 of the 4 peptides were mutated with high-risk (HR) cytogenetics [t(4;14), t(14;16), del17p, 1q21/25 gain and/or del13q]. WT1 was administered with mance s. 2 wks after SCT and q2 wks thereafter x 6 doses. GM-CSF was given on days -2 and 0 of each cycle. GMT of 4 peptides: WT1-A1: Y*MFPNAPYLPSCLES. 427-L (long): RSDELVRHHNMHQRNMTKL; 331-L: PGCNKRYFKLSHLQMHSRKHTG, and 122A1-L: SGQAY*MFPNAPYLPSCLES. 2 of the 4 peptides were mutated with high-risk (HR) cytogenetics [t(4;14), t(14;16), del17p, 1q21/25 gain and/or del13q]. 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-overlapping native WT1 peptides corresponding to the 2 heteroclitic peptide 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 (0.75-0.99) and 0.62 (0.42-0.97) respectively. Current median PFS: 23.6 mos (12.4 - not reached). No >2 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 SCT demonstrates favorable safety profile along with encouraging mPFS of currently 23.6 mos in this high-risk MM population. Clinical trial information: NCT01827137.

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Background: Given the unprecedented deep response rates with the novel agent induction, the role of high dose therapy (HDT) followed by ASCT in MM is not well defined. The presence of clonal CPCs has been associated with inferior outcomes in NDMM 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.

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. The incidence of hyperdiploidy was significantly higher in patients with CPC-/-, compared to those with CPC +/- and CPC+/. The rate of post-ASCT stringent complete response was 32% in the CPC-/- group, 30% in CPC+/+- group and 2% in CPC+/+ 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, 23 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.

Baseline characteristics of the trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Induction</th>
<th>Conditioning (HDT)</th>
<th>SDT regimen</th>
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<tr>
<td>Patel</td>
<td>R</td>
<td>M 200 x 2</td>
<td>MPA</td>
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<tr>
<td>Gay</td>
<td>R</td>
<td>M200 x 2</td>
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<td>Cavoo</td>
<td>Cy/ICdRd</td>
<td>M 200 x 2</td>
<td>MPM</td>
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Abbreviations: R, Lenalidomide; V, Bortezomib; C, Cyclophosphamide; M, Melphalan; P, Prednisone; d, Dexamethasone.

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Loss of heterozygosity in multiple myeloma: A role for PARP inhibition?

Methods: We analyzed 406 cases at all disease stages: MGUS (n = 7), smoldering MM (SMM, n = 30) newly diagnosed MM (NDMM, n = 71), relapsing MM (RRMM, n = 64) and relapsed MM (RLMM, n = 234). CD138+ plasma cells from BM aspirates (n = 234) were isolated using magnetic-activated cell sorting. DNA from these cells was subjected to single nucleotide polymorphism (SNP) genotyping and targeted next-generation sequencing (Adaptive Biotechnologies, Seattle, WA).

Results: We found evidence of HRD detected by LOH with higher LOH selecting for patients with poor outcome. The primary endpoint was overall response rate (ORR). Other endpoints included time to response (TRI), PFS, second primary malignancies (SPMs), and biomarkers. Results: Of 50 patients in cohort A, 29 (78.0%) demonstrated >5% dropout. Most (98.7%) were refractory to 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 PR). Clinical trial information: NCT02076009.
8029
Poster Session (Board #355), Mon, 8:00 AM-11:30 AM
HDAC11 as a candidate therapeutic target in multiple myeloma. First Author: Allison Distiller, H. Lee Moffitt Cancer Center, Tampa, FL
Background: Histone deacetylase (HDAC) inhibitors (HDI) have a therapeu-
tic niche in multiple myeloma (MM) due to their ability to salvage proteasome inhibitor and immunomodulatory drug responsiveness in re-
fractory patients, thus raising interest in this therapeutic class. Selective HDI may further improve therapeutic efficacy. Methods: B cell lymphopoi-
esis was evaluated using Tg-HDAC11-eGFP mice expressing eGFP regulated by the HDAC11 promoter and congeneric mouse strains deficient in HDAC11 expression globally (B6.HDAC11-/-) or targeted to the B cell lineage (C57B16.HDAC11-/-). Molecular and pharmacologic means were used to impair HDAC11 in established MM cell lines. Viability was measured by activated caspase-3, AnnexinV/PI (Apo) staining, and CCK-8 viability assay. Subcellular localization changes induced by HDAC 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 pe-
riphy. PC depletion in C57B16.HDAC11-/-mice suggests active inheritance 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 bor-
tezomib (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 cell viability. However, QS had no effect on RPMI-8226 cells activated caspase-3 and reduced viability by Apo staining. PLA of MM cell lines showed a novel interaction between HDAC11 and IRF4, an es-
sential regulator of PC differentiation and MM survival, unmasking a po-

tential 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 reg-
ulating 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 Aksad, 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 com-
parative efficacy and cost effectiveness has not been estimated. Methods: Network meta-analysis (NMA) and Bücher method were used to identify a group of SMM patients at high risk (ie. > 50% risk at 2 years) of organ damage. However rates of progression for FLC 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 FLC> 100 and 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 FLC range from 30% to 98%. Reasons for the discrepancy include selection/referral bias, patient heterogeneity, and lack of consider-

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: Aji 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 FLC 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 FLC> 100 and BMPC> 60% in our patient population and also to de-
termine the significance of hsp27 and FLC evolution using GBTM. Methods: We retrospectively investigated the predictive value of these events, network meta-analysis [NMA] and Bücher method were used 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 FLCR during the first 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 1 year vs 10 years 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 a median TTP of 27 months versus the remaining 75% who had no increase had a median TTP of 84 months (log rank p = 0.0043). Conclusions: Our results not only confirm a more modest 52% 2 year risk of PD with an FLCR > 100 and FLCR > 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 1.37 years. 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. Gonsales, Division of Hematology, Mayo Clinic, Rochester, MN

Background: Human adipocyes can contribute directly to the intra 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 with a BMI known at 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 < 0.001). Upon limiting the analysis to only SMM pts without MDEs at initial evaluation (N =187), the 2-year progression rate of SMM to MM 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.

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: Narjuz 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 cell cytotoxicity. However, there is lack of studies testing 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 a ≤ 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 group, but it was not statistically significant (170 vs. 106 months, p = 0.10). In a multivariable model, only elevated BMI (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 plus 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, q2w for cycles 4-8, and q4w thereafter). Elderly pts received a reduced dexamethasone dose (20 mg once weekly). Results: In POLLUX, 292/26 (DRd) and 352/25 (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, 235/25 (DVD) and 352/25 (Vd) were ≥ 75 y, with 89% and 94% having ECOG status ≤ 1, respectively. Upon limiting the analysis to only SMM pts, 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 NCT02076099.

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: Runzhoe 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 cancers. Gambogenic acid (GNA) is one of the natural compounds isolated from gamboge and has demonstrated advantages such as a more potent antitumor effect and less systemic toxicity according to early investigations. In this study, we hypothesized that GNA could synergistically demonstrate plasma cells cytotoxicity. However, there is lack of studies testing 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 group, but it was not statistically significant (170 vs. 106 months, p = 0.10). In a multivariable model, only elevated BMI (P = 0.013) was statistically significant in predicting for a 2-year progression to MM.

Conclusions: Metformin use was associated with a better PFS and higher CR after SCT in elderly (>75 y) pts from these phase 3 studies. 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, 235/25 (DVD) and 352/25 (Vd) were ≥ 75 y, with 89% and 94% having ECOG status ≤ 1, respectively. Upon limiting the analysis to only SMM pts, 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 NCT02076099.
**Hematologic Malignancies—Plasma Cell Dyscrasia**

**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 Lentzs, 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/m² SC bortezomib on days 1, 4, 8, and 11; 20 mg PO/dV 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 on 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) LOTs. 66% were previously treatd with bortezomib and 21% were refractory to lenalidomide in their 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, 0.25-0.43; 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 >95% vs 29% and <0.05% vs 10% for CR and MRD-negative rates, respectively). 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: Phillip 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 Rx. **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 Rx 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 Rx 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 resulted in a significant improvement in PFS vs PBO and improved the Rx 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: NCT00114103.

**8038**

**Poster Session (Board #364), Mon, 8:00 AM-11:30 AM**

**Daratumumab-based combination therapies (DCT) in heavily-pre-treated 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 ≥4 cycles of DCT (D/Pd, D/Rd, D/Vd) were included. Time 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 0 (0-2), 72% had 3 or more prior lines and 22% (56%) had previous D/Pd, D/Rd, and D/Vd respectively. Eighteen (14%) pts received ‘other’ Rx. Median time to first response (=PR) was 3.1 mos (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 mos (CI 4.2-6.1). The median duration of response was 6.1 mos (CI 5.1- not reached (NR)). Median progression free survival (PFS) was 5.5 mos (CI 4.1-7.8) and median time to next therapy (TTNT) was 9 months (CI 5.9 mos (CI 4-14.9) 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 pts who were refractory in quadruple-refractory pts, reflecting the challenges encountered in managing heavily-pre-treated, 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 recent study recently identified that the breast cancer cell line MDA-MB-231 utilizes Sema4D to create osteolysis (Yang Y et al, PLOS One 2016). We sought to investigate if myeloma cell lines with osteocytes increases the expression of Sema4D mRNA in both osteoblasts and osteoclasts.

**Methods:** Levels of Sema4D produced by osteoclasts. Myeloma bone disease is characterized by osteoclast activation utilizing Sema4D to suppress bone formation in multiple myeloma. There have been previous data that Sema4D is increased in the serum of patients. There 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 resulted in a significant improvement in PFS vs 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: NCT00114103.

**OCT, Unadjusted**

<table>
<thead>
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<th>OS</th>
<th>NR vs 7.9</th>
<th>58.4 vs 28.9</th>
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<tbody>
<tr>
<td>PFS</td>
<td>0.56 (0.42-0.76)</td>
<td>0.58 (0.46-0.73)</td>
</tr>
<tr>
<td>PFS</td>
<td>0.58 (0.46-0.73)</td>
<td>0.50 (0.39-0.63)</td>
</tr>
<tr>
<td>IPE</td>
<td>0.48 (0.33-0.63)</td>
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</table>

*Data are median, mos; HR (95% CI). *Bootstrapped 95% CI.*
analyses showed generally similar PFS and OS improvements across subgroups regimen. Preliminary analysis of 2nd PFS suggests no impact on the efficacy of 2nd therapy. These data from a largely community-based setting confirm results on outcomes in patients (Pts) with newly diagnosed multiple myeloma (NDMM) using the large prospective community-based Connect MM registry.

Methods: The SLR searched MEDLINE, Embase, and the Cochrane Library for RCTs investigating the efficacy of treatments for RRMM (to August 2016). NMA results.

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%) analysis criteria. Data cutoff was Jan 7, 2016 (median follow-up of 39.3 mo).

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 (K), lenalidomide+dexamethasone (KD), and carfilzomib+dexamethasone (KD). 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 DRd (ClinicalTrials.gov Identifier: NCT01568868, NCT01803911, NCT01803911, NCT01803911). PN, PROs, and PFS in ASPIRE; ENDEAVOR.

Conclusions: In ASPIRE, PN was similar for KRd vs Rd. PFS was longer with Rd and KRd vs Rd and Vd, respectively, including in pts with BL grade ≥2 PN. Improved pain and neurotoxicity with K may be attributed to better disease control and/or lower rates. Clinical trial information: NCT01568868, NCT01803911.

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-Well 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/m²lenalidomide (Rd vs the largest prospective community-based 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 ASCET 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%) 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, 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. Data from a large community-based setting confirm results from randomized phase III trials. Clinical trial information: NCT01803911.

<table>
<thead>
<tr>
<th>LEN</th>
<th>No MT</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>50.3</td>
<td>30.8</td>
</tr>
<tr>
<td>3-yr PFS</td>
<td>56%</td>
<td>42%</td>
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<tr>
<td>Median OS, mo</td>
<td>50</td>
<td>NR</td>
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<tr>
<td>3-yr OS</td>
<td>85%</td>
<td>70%</td>
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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Racial differences in abnormalities by FISH in minorities with multiple myeloma: A single-center experience. First Author: Miguel Gonzalez Velez, 8044 Poster Session (Board #370), 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) (Pazmiño et al, ASH meeting 2021). We aimed to explore how racial differences in FISH abnormalities using the largest cohort of m to date. Methods: CD-138 selected FISH was done on 799 consecutive patients (pts). Pts without symptoms for MM, and who had >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), del13q, del17p. Results: Compared to W, M had more abnormalities in IGH r, t(4;14), t(11;14), t(14;20), t(14;16), del13q, del17p, 1q21. Conclusion: We had significant differences in FISH abnormalities between W and M. There was no difference in high risk FISH abnormalities between W and M. M had more abnormalities in high risk FISH abnormalities compared to W. 

Conclusions: Conclusions: We had significant differences in FISH compared to W. M had more IGH r and t(11;14) than M. 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 45% (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 in 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), bilirubin (p=0.1), 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.

<table>
<thead>
<tr>
<th>Organ Site</th>
<th>Response</th>
<th>n (Percent of Responders)</th>
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<tbody>
<tr>
<td>Cardiac</td>
<td>Complete OR</td>
<td>51% (n=308, N=600)</td>
</tr>
<tr>
<td>Renal</td>
<td>Partial OR</td>
<td>36% (n=22, N=110)</td>
</tr>
<tr>
<td>Liver</td>
<td>Complete OR</td>
<td>25% (n=22, N=110)</td>
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<td>Gastrointestinal</td>
<td>Complete OR</td>
<td>24% (n=205)</td>
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<tr>
<td>Autonomic</td>
<td>Complete OR</td>
<td>24% (n=205)</td>
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*Including pts who died at landmark time-point

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**Hematologic Malignancies—Plasma Cell Dyscrasia**

**8049** Poster Session (Board #375), Mon, 8:00 AM-11:30 AM

Outcomes according to involved 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 radiation treatment (73.5 vs 64.8%; p=0.07), in mayo stage I / II / III / IV (32.9% vs 23% vs 27.3% / 16.8% vs 43.6% vs 22.9% / 18.1% / 15.4%; p=0.1), with bone marrow plasma cells >10% (24.2 vs 30%; p=0.2) and presence of hIFLC2 (14.84 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 hIFLC2 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; 2.4, 5.6) vs 5.6 y (95% CI; 4.7, 7.1); P<0.0001 and OS (7.8 y; 95% CI; 6.4, 9.9 NR vs 95% CI; 5.9, 9.9; 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.

**TPS051** 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. Leschuk, 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, which can provide a viable IMT platform. Reinforcement 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.
Background: Multiple myeloma (MM) cells may evade immune surveillance by expressing immune responses through the PD-1 path- way, via the expression of PD-L1. 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 (Dex) for RRMM. Dexamethazum (elo), an anti-SLAMF7 monoclonal antibody, directly activates normal 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 \( \geq 2 \) prior lines of therapy (LoTs) that included an IMiD and proteasome inhibitor, each for \( \geq 2 \) 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 stage (I–II vs III). Pts in the Pd arm may crossover to the Pd arm at disease progression sites in 13 countries. Co-primy 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: 2969–304. 2. Lespert et al. JCO 2016;34:2698–704. 3. Bezman et al. Haematologica 2016;101:161–2. 4 [S450] Study supported by Roche and Genentech. A: Gill, Caudex, funded by BMS. Clinical trial information: NCT02726581.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 carfilzomib, 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) 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.

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 ~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.
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 re-...

Methods: Completely randomized 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/m2 Day 1 and Day 8) plus cisplatin (75 mg/m2 Day 1) every 3 weeks for 4 cycles. Stratification factors were lymph node status (pN1/N2) and EGFR mutaton 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) 22.3 to 35.2) 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/N0) 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.
Lung—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers

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: Shinsh 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 pembrolizumab in ES-SCLC pts who had response/stable disease after 4-6 cycles of platinum/etoposide. Methods: Pts were required to begin pembrolizumab within 6 weeks of completion of chemotherapy, with resting scans no more than 3 weeks prior to start of pembrolizumab. Prophylactic cranial radiation was permitted. Pts were treated with pembrolizumab 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 PD-L1. Blood for circulating tumor cells (CTCs) was collected prior to first, second and third cycle of pembrolizumab. Results: Of the 49 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 cycles of pembro was 4 (IQR 3–6). 35 pts had measurable disease at study entry. The disease control rate with pembrolizumab 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 7 months (90% CI: 6.1–15.2). 11 pts are still on therapy (3-20 cycles). The median CTC prior to pembrolizumab 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). PD-L1 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 pembrolizumab did not improve PFS in these patients but favorable OS suggests that some SCLC patients can benefit from maintenance pembrolizumab. Biomarkers to identify patients most likely to benefit from pembrolizumab 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/m² and 100 mg/m²) 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 68% 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: 0.81 (90% 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). Saliency 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.

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-naive malignant pleural mesothelioma (MPM) patients (pts). 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 placebo-controlled trial of Nintedanib + pemetrexed/cisplatin (PEM/CIS) vs placebo in patients (pts) with malignant pleural mesothelioma (MPM).

First Author: Arnaud Scherpereel, University Hospital of Lille, Lille, France

Results: 202 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] m vs 15.2 [12.2–23.6] m). 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 0.28-0.87; 2-sided p=0.006) with a mPFS gain of 4.0 months (mPFS (95% CI): 9.7 [7.2–12.4] m vs 5.7 [5.5–7.0] m). Improved forced vital capacity, objective response rates and duration of response were also observed with N vs P treatment. Drug-related adverse events (AES) in N vs P-treated pts were 97.7% vs 96.7%. 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 dose 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 therapy 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.
Outcomes of anti-PD-1 therapy in mesothelioma and correlation with PD-L1 expression.

**First Author:** Gareth Rivaland, Olivia Newton-John Cancer Research Institute, 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 the entire cohort treated with PD-L1 inhibitor Nivolumab (PDCD1LG1) expression. Methods: Patients (pts) with unresectable pleural or peritoneal MM were treated with Nivolumab. Dose escalation was assessed by IHC clone E1L3N (Cell Signaling Technology). PD-L1 expression was assessed with IHC clone E1L3N (Cell Signaling Technology). 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-L1 blockade. Clinical trial information: NCT02259621.

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-L1 blockade. Clinical trial information: NCT02259621.

**Outcomes of anti-PD-1 therapy in mesothelioma and correlation with PD-L1 expression.**

**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 - IIA 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 prep without progression or toxicity. Among the 21 attempted resections, 1 tumor was unresectable. 9/21 (43%, 95% CI 24.6-63%) had a major pathologic response (< 10% viable tumor cells in resection specimen). With a median follow-up of 16 months, 15/22 (68%) remained 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 enrichment 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-L1 blockade. Clinical trial information: NCT02259621.

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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) Locoregional Lung Cancer 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 biobanked of resected stage I-II 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; 51/24/43% adenocarcinomas (AC) / squamous cell carcinoma (SCC) / large cell carcinoma (LC). Other. Median RFS/TTR/OS rates were 93/83/68 months (AC: 88/77/58, SCC: 84/65/57, LC/other: 89/63/52). PD-L1 prevalence was 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 LC/other: 53%, 95%CI: 50-56%). The cut-off of 20% prevalence was 34%, 95%CI: 32-36; PD-L1 1% positivity was a significant predictor only for AC: HR: 0.83; 95%CI: 0.69-0.97, HR: 0.83; 95%CI: 0.68-1.01, HR: 0.93; 95%CI: 0.83-1.01. PD-L1 5% positivity was a significant predictor only for AC: HR: 0.75; 95%CI: 0.64-0.90, HR: 0.75; 95%CI: 0.62-0.91, HR: 0.84; 95%CI: 0.70-0.99. 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 outcomes overall and by histology type.

**Conclusions:** PD-L1 positivity (1% and 5% cut-offs) is present in more than one third of resected NSCLC and was associated with a better prognosis for AC patients.

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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, Hamamatsu, Japan

**Background:** Recent genomic studies of small-cell lung cancer (SCLC) have identified a series of targetable genomic alterations and their clinical features, contributing to the development of novel targeted therapies. First Author: Keith Kerr, Aberdeen Royal Infirmary, Aberdeen, United Kingdom

**Methods:** Comprehensive genomic analysis of 1006 SCLC cases was performed using the Oncomine Comprehensive Assay, enabling the simultaneous detection of 5000 tumor genes and 1600 gene expression profiles. Genomic alterations were detected using targeted next-generation sequencing (NGS). The samples were subjected to a next-generation sequencing (NGS) analysis (MinION, Oxford Nanopore Technologies) and subjected to cross-validated classification models to identify genomic signatures associated with specific clinical outcomes.

**Results:** The NGS analysis also showed that 62 (23%) of cases had at least one targetable genomic alteration, 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 < 0.0001) were significantly more frequent in the EGFR type compared to the others. The KRAS type showed significantly poor prognosis free of progression (PFS) of the first-line chemotherapy compared to the others (median PFS 1.2 vs. 6.1 months, respectively; p < 0.0001). Mutations in the PIK3/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 gedotirizib labeled "EAGLE-PAT" (UMIN000020585).

**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.

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Analysis of circulating tumor DNA in localized lung cancer for detection of molecular residual disease and personalization of adjuvant strategies. First Author: Aadil 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 personalized adjuvant treatment approaches but has not been explored in lung cancer.

**Methods:** We applied CAPP-Seq, a novel ultra-sensitive next-generation sequencing based ctDNA quantification method, to pre- and post-treatment blood samples from a cohort of 41 patients treated via chemoradiation, radiotherapy and surgery for stage I-II 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. 65% for MRD- patients; p < 0.0001) and 3-year overall survival (5% vs. 87% for MRD- patients; p < 0.0001).

**Conclusions:** Our results indicate that ctDNA analysis accurately detects MRD in localized lung cancer patients, could facilitate personalized adjuvant treatment at early time-points when disease burden is minimal.
A phase II study of pembrolizumab for patients with previously treated advanced thymic epithelial tumor. First Author: Jinhun Cha, 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 an objective response rate of 24.2%. The median progression-free survival was not reached for T and 6.2 months for 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 3-5 included immune-related adverse events (2.4%) and other grade 3-5 adverse events (12.1%). Conclusion: Pembrolizumab showed promising antitumor activity in refractory or relapsed TET. The relatively high incidences 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.
Temporal trend in the use of surgery in the management of stage IIA non-small cell lung cancer (NSCLC) between 2000-2013: A SEER analysis. First Author: Veeck, Jey, University Of Toledo, Toledo, OH

Background: The optimal treatment of patients with Stage IIA 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 IIA lung cancer diagnosed between 2000-2013. Methods: The study included patients with Stage IIA 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 27,657 patients with Stage IIA 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 (RS24) 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 (RS24) from 2000 to 2010 rose from 34.7% to 43.2% (z = -4.89). The RS24 for patients who received surgery rose from 55.3% in 2000 to 77.6 % in 2010 (z = -3.58). Changes in RS24 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 IIA 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.

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 ICER were estimated. Multivariable analysis, with OS HR 0.51 (95% CI 0.39-0.66) in favor of AC (n = 339). One- and 5-year survival in AC group versus non-AC 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: AC after thoracic surgery for NO-1 NSCLC with SBM is associated with improved OS in this analysis.

Survival benefit of systemic chemotherapy given as adjuvant (ACT) after thoracic surgery for NO-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 prognostic 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, 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 IIA 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.
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 malignancy 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 710 patients and somatostatin receptor scintigraphy (SRS) positive in 1520 and in 4/11 there was avidity with both. 20 patients were treated with somatostatin analogues predomi- nantly for CENCS. 11 patients treated with an anti 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 or 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 (ONSLC). 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 ONSLC. 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 13419 with resected ONSLC. A higher proportion of patients with ONSLC 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 ONSLC (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 resected IA LCNEC may 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 ONSLC.

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 1 phase dose-escalation (NCT02289650) evaluated V combined with Cb/E. Methods: Pts (≥18 years with ED-SCLC or other advanced solid tumors with n ≥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/m2 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 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 hematological toxicities. 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) of 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 Xiang, 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, single arm protocol aimed to compare the erlotinib and etoposide/cisplatin with concurrent radiotherapy (RT) in pts with EGFR-mutant. Methods: Histopathology/ cytology confirmed stage IIIA/IV unresectable NSCLC pts (age 18-75) with ECOG PS 0-1 and EGFR wild type or EGFR 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 (20Gy/5day, 5days/ week for 6 weeks from first day of erlotinib). EP arm was treated with sequential etoposide (50 mg/m² IV days 1-5, 29-33) and cisplatin (50mg/m²IV day 1, 29, 36) and RT (from 1st day of 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. Comparability. Continuous dosing of EP was significantly improved (27.6% vs 6.41 months; HR 0.21, 95% CI: 0.004-0.64; P<0.001). ORR and DCR were 60.0% vs. 38.1% (P=0.217), and 65% vs. 47.6% (P=0.390), 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.

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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 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/m² 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 = 98; CRT arm, n = 102) 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: UMIN000005993.
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 1, 2, and 3 NSCLC, respectively. ALK+ pts were distributed across all stages: 10 (34%) stage 1, 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.

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). Immunological and clinical data were analyzed by means of the 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, FORXP3, and PD1 counts in the periphery and the 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 = 0.8e-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 III disease vs stage IIIV (p = 0.001). For all immune markers in PR samples, an average has higher counts vs tumor core (p < 0.0011), and this difference (suppression score) is higher in stage IIIV IIS samples vs stage II for CD3, CD4, and CD8 (all p < 0.04) and for FORXP3 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 (>I=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 (>4 cm) – 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)lateral resection post-neoadjuvant chemotherapy (CxT) or concurrent chemoradiation (CxRT) were included. Primary outcomes were overall and disease-free survival (OS and DFS). Results: Demographic 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 (QX 30% vs 31%, p = 0.275). Recurrence rates (QXT47% vsQXR48%, p = 0.799) and patterns were identical (Local: QX 10% vs CxRT 8%; and Distant: QX 30% vs CxRT29%, 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 (QX 40% vs CxRT 42%, p = 0.364) and DFS (QX 30% vs CxRT 31%, p = 0.332) Multivariable analysis identified pneumonectomy (HR1.66, p = 0.001) and ypN2 (HR1.84, p = 0.001) to be associated with OS. Survival Conclusions: Both treatment strategies produce equivalent and better than expected outcomes compared to historical controls for IIIA NSCLC.

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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 Ila, 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 Ila cases. Results: In multivariate analysis, independent factors for CSS were (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 Ila 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 ongoing.

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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.

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.

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.

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).
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/III NSCLC and assess the impact of changes in causes of death over time. Methods: Using the VA Central Cancer Registry, we identified patients diagnosed 2001-2005 with stage I/III 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 (Y1), 5 year (Y5), and 10 year (Y10) mortality. We compared causes of death at 1 Y versus 5 Y 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 (<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 adenosquamous cell carcinoma (88%) and squamous cell (67%) 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 ≥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: 1.56 (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/III 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 IIA 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 IIA NSCLC (a patient population with no optimal biomarker to guide post-surgical 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 post-surgery (cases) and 15 patients have not relapsed with a minimum of 5 years post-surgical 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 by events in 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 OS (p = 0.015) and shorter DFS (p = 0.008). A highly significant 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 launched to study the safety and efficacy of V/P/C CRT in the treatment of Stage III NSCLC. Methods: Subjects without prior NSCLC therapy suitable for definitive CRT received V plus C AUC 2 + 45 mg/m2 weekly + 60 Gy over 6-9 weeks. V was escalated from 60 mg BID to a maximum planned dose of 120 mg BID. Enrollment followed by consolidation chemotherapy of V 120 mg BID + C AUC 6 + 200 mg/m2 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 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 AEs were observed including 8 with reasonable attribution to V but outside the DLT window including G3 febrile neutropenia (2), G3 dehydration (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/P/C-based CRT followed by VCP 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 IIb study of tepotinib in EGFR-mutant/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 IIb 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 EGFR PS 0–1. Tumors had to express EGFR with an activating mutation be resistant to EGFR TKI therapy (progression on Iressa® or Tarceva® and/or disease progression on Gleevec® or Sorafenib® 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 adverse events (TRAEs), mostly grade 1–2 and most commonly diarrhea (12), rash (8), and amylase increase (6). Grade ≥3 TRAEs were increased amylase (n = 4), increased lipase (3), neutropenia (1), and hyperglycemia (1). The most common overall TRAEs were G1/2 of diarrhea (7/10 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 IIb trial is randomized to 156 pts with c-Met+/T790M– tumors who have failed first-line EGFR TKI 2:1 to tepotinib + gefitinib or pemetrexed + cisplatin/ carboplatin. Clinical trial information: NCT02864992.

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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 ≥ 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.

8550 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 ± 36.74% 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 > 65, p-value = 0.0208) and smoking status (p = 0.048). 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.

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 programmed 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 in association with clinical features, tumor-infiltrating lymphocytes (TILs), HLA class I (I-2 microglobulin; B2M) expression, molecular alterations, and patient outcomes. Results: There was expression of PD-L1 in 89 (34.1%) and IDO1 in 74 (28.4%) 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. TILs PD-L1 expression and abundant CD8+ were inversely associated with a loss of B2M membrane 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 mutations (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 survival (PFS) and overall survival (OS), while IDO1 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, CTLA-4/HLA 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. This may explain the lack of efficacy of IDO1 as a therapeutic target.
8553 Poster Session (Board #293), 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 prolonged arginine deprivation (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, with tumoral ASS1 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 biopsyed 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. Tumor 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, without epithelioid disease. Based on these data the ATOMIC-II phase 2/3 trial has started comparing ADIPEMCIS versus PEMCISPlacebo, focusing on pts with non-epithelioid MPM. Clinical trial information: NCT02029690.

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 15 cohort members, with a long-term follow up (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 ME; median age 70; 7%, complete pleurectomy decortication (PD) 10%, extended PD 60%, partial PD 10%, unsectectable 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, 30%; 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 increased 3-59% in 41% patients. DCR increased 1-61% in 50%. Biological correlates of treatment included target inhibition (75% pFAK reduction); tumor immune microenvironment changes: increased naive (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 and did not alter resectability, or mortality compared to prior series. Of the 19 patients who 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, survival, death, years post diagnosis, and at least 3 months post, the diagnosis index date. Patients with other 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, comorbidities 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 95.6%, 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 effusion (16.5%), followed by pleural effusion (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.
Biomarkers of pembrolizumab (P) activity in mesothelioma (MM): Results of the NIBIT-MESO-1 trial.

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 no responses, the study proceeded to Part B (N = 30), using a biomarker enrichment strategy if a threshold was found. Nanostar 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/NO; 74%/21%/5%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, hynpertonalgia, 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 GE patients, 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.

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Poster Session (Board #297), Sat, 8:00 AM-11:30 AM
A nonrandomized confirmatory phase III study of sublobar surgical resection for peripheral lung cancer: a global perspective for patients with limited stage small cell lung cancer (SCLC) and non-SCLC.

Methods: A total of 192 patients with clinical stage I SCLC (n = 774, 15.9%), surgical resection without chemotherapy (n = 423, 8.7%), lobectomy and pneumonectomy (n = 28.8%) and pneumonectomy (2.8%) with 5-year survival of 13.9%). 5-year survival for each group was 47%, 36%, 22% and 11% respectively, (p < 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 < 0.001). Multivariate analysis identified that elderly (age ≥ 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 ≥ 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.

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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 outcomes. However, tumors from surgery are not available for most 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 cfDNA 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 (ctDNA) was associated with heavy tumor burden (R = 0.7, p = 0.001). Moreover, patients with high ctDNA fraction in cell-free DNA (cfDNA) was associated with heavy tumor burden (R = 0.7, p = 0.001). Moreover, patients with high ctDNA fractions in cfDNA had an overall survival (OS) of 9.9 months. Further analysis showed that high ctDNA fraction in cell-free DNA (ctDNA) was associated with heavy tumor burden (R = 0.7, p = 0.001). Moreover, patients with high ctDNA fractions in cfDNA had an overall survival (OS) of 9.9 months.

Conclusions: For patients with stage I SCLC, cfDNA analysis offers a promising way to depict the molecular profile in patients with SCLC. Moreover, these findings highlight the potential clinical utility of ctDNA analysis to improve treatment outcomes for SCLC patients.

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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 as >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 <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% vs 52%, p=0.045 and 28% vs 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.

Postoperative radiation for tumor control and overall survival in thymic epithelial tumors (TE): A matched-pair analysis. 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 expression, tumor regions with different morphologic appearances may have very similar genomic profiles while tumors with the same morphologic 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 different 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, but not small-cell component in one patient. Conclusion: 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.
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-related 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). These 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 hypothyroidism. 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 showed 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 28-8), 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, Nanostinger and PD-L1 expression is ongoing and updated survival will be presented. Clinical trial information: NCT02364076.

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 wild-type EGFR and ALK, treatment is permitted. Adjuvant therapy is mandatory for non-squamous histology and may have a higher risk of intrathoracic recurrence.

Conclusions: P has activity in patients with thymic carcinoma. irAEs are more frequent than in other tumors. Further analysis of NGS, Nanostinger and PD-L1 expression is ongoing and updated survival will be presented. Clinical trial information: NCT02364076.

**TPS8575**

Poster Session (Board #311a), Sat, 8:00 AM-11:30 AM

EAS1424 adjuvant nivolumab in resected lung cancers (ANVIL): The newest study in the ALCHEMIST platform. First Author: Jamie E. Chua, Memorial Sloan Kettering Cancer Center, New York, NY

**TPS8576**

Poster Session (Board #311b), Sat, 8:00 AM-11:30 AM

Methods: EAS1424 is a phase III clinical trial platform that consists of integrated protocols: ALCHEMIST Screening (A151215; NCT02194738), ALCHEMIST-EGFR (A081105; NCT02193282), ALCHEMIST-ALK (A4512; NCT02919992), and ALCHEMIST-nivo (EAS142; NCT02959946). In ALCHEMIST-Screening, up to 8,000 patients with pathologically confirmed stage IB (~ 4 cm)-IIA 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 wild-type EGFR and ALK, treatment is permitted. Adjuvant therapy is mandatory for non-squamous histology and may have a higher risk of intrathoracic recurrence.
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 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 III B/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 ≥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.

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, concurrent administration of monoclonal antibodies, and escalation of radiation therapy (RT) dose—have not improved these outcomes. PD-L1 checkpoint inhibitors represent an effective treatment for advanced NSCLC and may enhance RT-associated anti-tumor immunity. RTQ505 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/m² IV on Days 1, 8, 29, and 36, and etoposide 50 mg/m² IV on Days 1–5 and 29–33. This regimen was selected to (1) minimize risk of pulmonary toxicity and steroid requirement, 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 >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.

Background: Ensartinib is a novel, potent anaplastic lymphoma kinase (ALK)-positive TKI. Ensartinib was selected to (1) minimize risk of pulmonary toxicity and steroid requirement, and (2) improve OS and PFS after completion of chemoradiation, eligible patients 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 ≥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 ≥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.

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 1.02 – 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 ≥10% of viable tumor tissue based on surgical resection. Secondary end points include overall response rate by status of mutation load, neoadtgen 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.
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.

Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers

TPS8581 Poster Session (Board #314a), Sat, 8:00 AM–11:30 AM

A phase III study of rovaipatumab 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 embolizes 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 carboplatin 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 ligand which is over-expressed on TICs. DLL3 is highly expressed in SCLC TICs. DLL3 is highly expressed in SCLC but not normal tissue. Rovaipatumab tesirine (Rova-T) is an antibody-drug conjugate composed of a DLL3-targeting IgG1 monoclonal antibody tethered to a DNA cross-linking toxin. Lysine-linked arginine deiminase (ADI) is an enzyme that deiminates arginine to citrulline in tumor cells. ADI has been shown to be a viable therapeutic target in small cell lung cancer in a phase 2b study (NCT02709512). Methods: Approximately 740 ED SCLC pts will be enrolled to include ~480 pts with high DLL3 expression. Pts will be randomized to receive weekly Rova-T or placebo. Primary endpoints are disease control rate (DCR) and OS. Preliminary data indicate that Rova-T reduces TICs and tumor burden. Results: Median progression-free survival (PFS) was 2.7 months for placebo and 7.7 months for Rova-T (p < 0.0001). Median OS was 9.3 months for placebo and 15.4 months for Rova-T (p < 0.0001). Conclusions: Rova-T improves progression-free and overall survival in this setting. This is a ongoing clinical trial of rovaipatumab tesirine maintenance therapy following first-line platinum-based chemotherapy in patients with extensive disease small cell lung cancer (ED SCLC). Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

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 synthase 1 (ASS1)-deficient malignant pleural mesothelioma (OS) rate of 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 (NCT02209690) 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.
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 2nd-line 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 (75 mg) i.v. q3w + CT (Arm 2); or CT alone (Arm 3). D (75 mg) i.v. q3w – T (6 mg) i.v. q3w + CT (Arm 1); 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/m²] i.v. on Days 1–3 q3w + carboplatin [AUC 5–6] i.v. on Day 1 q3w + carboplatin [AUC 5–6] i.v. on Day 1 q3w or cisplatin [75–80 mg/m²] 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 duration of response, disease control rate, time to progression, PFS, OS, and safety and tolerability. Recruitment is ongoing. Clinical trial information: NCT02937818.

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/m²] i.v. on Days 1–3 q3w + carboplatin [AUC 5–6] i.v. on Day 1 q3w or cisplatin [75–80 mg/m²] 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 with HER2-positive metastatic breast cancer (MBC) treated with a planned, ongoing phase 2 study (NCT02289833) of pts with previously treated HER2-overexpressing mNSCLC 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+. Pts had partial responses (20%, 95% CI 5.7–43.7) with a median duration of response of 7.3 months (range 2.9–8.3 months). Median progression-free survival (PFS) in IHC2+ and IHC3+ pts was 2.6 (95% CI 1.4–6.1) 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 (66%) 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 under way to refine markers for optimal pt selection. Clinical trial information: NCT02289833.

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 (METe14) non-small cell lung cancer (mNSCLC). 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 (METe14) skipping. We conducted a multicenter retrospective analysis of pts with METe14 NSCLC to determine if treatment with MET inhibitors impacts survival.

Methods: We collected clinicopathologic data on pts with METe14 NSCLC. Event-time distributions were estimated using Kaplan-Meier methods and were verified using the log-rank test. Aivariable Cox models were fitted to estimate hazard ratios. Results: Of the 148 pts with METe14 mutant NSCLC, the median age was 72 (range 43-88); 57% were women, and 41% were never smokers. The most common histologies were adenocarcinoma (72%), squamous cell carcinoma (7%), and large cell carcinoma (6%). Response to MET inhibition had a trend toward worse survival compared to MET wild-type tumors. 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). Fifteen of the 27 pts with metastatic disease who received at least one MET inhibitor (including crizotinib, glezatinib, 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 pts treated with crizotinib, the median progression-free survival (PFS) was 7.36 months. Conclusions: Forpts with METe14 NSCLC treated with a MET inhibitor was 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 METe14+ 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 (mNSCLC). First Author: Joshua K. Sabari, Memorial Sloan Kettering Cancer Center, New York, NY

Background: METe14 skipping alterations (METe14) 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 METe14 lung cancers and response to PD-L1-based immunotherapy.

Methods: Pts with METe14 mutant non-small cell lung cancers were 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 METe14 mutant lung cancers were identified. Seventy-two percent (72/100) were PD-L1 positive (PD-L1 score 5/10). Six patients were intratumoral PD-L1 positive and 10% (1/10) were intratumoral PD-L1 negative. Six patients were PD-L1 negative and 10% (1/10) were intratumoral PD-L1 negative. The median age for patients with METe14 and PD-L1 positive (1+/1+) tumors was 65 years (range 49-87); 60% (11/25) of patients were female; Male sex, 72% (18/25) adenocarcinoma, 24% (6/25) sarcomatoid carcinoma, and 4% (1/25) squamous cell carcinoma. Immuno-therapy was given to 15 pts; nivolumab (5), pembrolizumab (3), atezolizumab (2), durvalumab (1), and ipilimumab (1). A substantial proportion of NSCLCs harboring METe14 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 genetically defined subset of cancers. Further understanding of this subset may reveal important mechanisms of immunotherapy resistance in PD-L1 expressing tumors.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
9001 Oral Abstract Session, Tue, 9:45 AM-12:45 PM
Impact of atezolizumab (atezo) treatment beyond disease progression (TPB) 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 (HR: 0.76, 95% CI: 0.61-0.98; p = 0.02). Here we evaluate CIT beyond TPB, defined as post TPB PD or loss of clinical benefit per investigator or doc 75 mg/m² IV aq 3w until PD per RECIST. No crossover was allowed. Primary outcome measure: OS. Atezo TPB 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 lesion (≥ 30% reduction from new baseline at PD), 49% (83/168) had stable target lesions (best change between 20% and 30%); mOS was 20.7 mo (95% CI: 19.1, 22.3). mOS was not associated with increased safety risk. Conclusions: This is the first report from a Phase III study of CIT in NSCLC to evaluate 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.

9003 Oral Abstract Session, Tue, 9:45 AM-12:45 PM
IFC-TGFC-1101 trial: A multicenter phase III assessing a maintenance strategy determined by response to induction chemotherapy to continuation maintenance with pemetrexed in patients (pts) with advanced non-squamous (NSQ) NSCLC. First Author: Maurice Perol, Department of Thoracic Oncology, Centre Leon 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 failure. In the primary analysis, grade ≥ 3 hematologic toxicity 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 (CG: 142, P: 113) while 274 pts (58.9%) received maintenance in the CP arm. Median number of maintenance cycles was 5 for G and 4 for CP. 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 OS advantage was 0.81 (95% CI: 0.64-1.03; p = 0.09); median OS: 10.9m CG vs. 10.4m CP. Safety profile was as expected during induction chemotherapy. During maintenance, grade ≥ 3 hematologic toxicities 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-hematologic AE occurred in ≥ 5% of pts except for asthenia (3.9%). Partial response and 2.2% (n = 20) and 1.8% (n = 16) were reported. Pts in the CG arm had significantly lower risk of OS (HR 0.82, 95% CI: 0.68-0.97; p = 0.018). Conclusions: Adapting maintenance strategy according to response to induction chemotherapy does not improve patient outcome. Clinical trial information: NCT01631136.
Efficacy and safety results from AvaALL: An open-label, randomized phase II 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: Jafar Bennoua, Institut de Cancérologie de l’Ouest, Nantes, France

Background: The role of treatment with Bev beyond PD is unclear in the multilines treatment strategy of advanced NSCLC.AvaALL(NCT01351415), a multinational, open-label, randomized phase II trial, assessed continuous Bev and SOC beyond first-line PD (P1) in pts with NSCLC following first-line PD 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 (P2D) and third PD (P3D), pts received third-line or fourth-line SOC > Bev treatment, respectively. Primary endpoint was OS duration. Secondary endpoints were OS rates (6, 12, and 18 mos) progression-free survival (PFS) from PD1 to P2D/P3D to P2D, 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 11.6 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 50% higher in the Bev arm vs SOC alone at 6-, 12- and 18-month follow-up (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, HR 0.74, 90% CI 0.65–0.83; p = 0.0047). ORR and DCR were slightly higher in the Bev arm versus the SOC arm (Bev 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.
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.

**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 hybridization 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-ALKv1 (E13; A20), 20 (8%) EML4-ALKv2 (E20; A20), 204 (32%) EML4-ALKv3 (E6; A20), 78 (12%) other EML4-ALK, and 102 (16%) non-ALK 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 = 0.0002), 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 = 0.0068) 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 ALK non-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.

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**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. Blakey, 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 targeted 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, CDKN1A 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 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 tumor exposure (mean 1.2 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 genomic 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.
Safely 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-L1 (+/- anti-CTLA-4) between 4/2011 to 5/2016 who had a treatment delay of at least 1 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 with concurrent disease progression were excluded.

Results: Among 482 pts treated, 71 (14.7%) had a 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-L1 therapy. In retreated pts, the same irAE recurred in 10/39 (26%), a new irAE occurred in 9/39 (23%), and 13/39 (33%) had no subsequent new irAEs. The rate of 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 (>3 months) in treatment course (16/24 [67%] vs 3/15 [20%], p = 0.007). The rate of recurrent/new irAEs in 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 occurred. Few objective responses occurred following retreatment.

Efficacy and safety of epacadostat plus pembrolizumab treatment of NSCLC: Preliminary phase 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 I/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 I/2 NSCLC cohort. Method: NSCLC pts with prior platinum-based therapy (tx) and no prior checkpoint inhibitor tx were eligible. Phase I dose escalation tx was E (25, 50, 100, 300 mg PO BID) + P (2 mg/kg or 200 mg IV QW); MTD was not exceeded. E (100 mg BID) + P (200 mg BID) was chosen as the Phase II dose for pts in the phase I/2 cohort. Efficacy was evaluated by tumor proportion score (TPS % viable tumor cells, PD-L1 staining) ≤ 50% and ≥50%) and by prior lines of tx in RECIST 1.1 evaluable pts. Safety was assessed in pts receiving ≥1 E + P dose. Results: As of 29/06/2021, 43 pts (phase 1, n = 12; phase 2, n = 31) were evaluated. Median age was 65 years, 58% of pts were women, 12% were never smokers (8%), ≤2 prior lines of tx (84%), and no prior TKI tx (95%). 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 results were available in 28/40 efficacy-evaluable pts. ORR and DCR for pts with AUC ≥ 50% vs <2 prior irtx were 43% (3/7; all PR) and 57% (4/7; 1 SD), respectively, for pts with PFS ≤ 50% and ≥2 prior irtx, 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 (15%), arthralgia (9%), and increased AST (9%); 16% of pts had grade ≥3 TRAEs, and increased ilpase (asymptomatic) was the only grade ≥3 TRAE that occurred in >1 pt (n = 2). Two pts discontinued due to TRAEs grade 3 increased AST (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.
STK11/LKB1 co-mutations to predict for de novo resistance to PD-1/PD-L1 axis blockade in KRAS-mutant lung adenocarcinoma. First Author: Ferdinandas Skouliadinis, 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 SUT2/CACS 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 ELLN N1 HSC assays and quantified as percent of staining tumor cell membranes. Isogenic derivatives of the LKR10 KRas234/12C1 murine LUAC cell line with CRISPR/Cas9-mediated Lkb1 knockdown 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%) subgroups (P = 0.005, Fisher’s exact test). PFS was significantly longer in KL compared to KP (median 3.8 vs 4.4 wks, HR 0.43, 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.

Osimertinib compared to docetaxel-bevacizumab as third-line treatment in EGFR T790M mutated non-small cell lung cancer. First Author: Keke Nie, Qilu Hospital, China University of Pittsburgh Medical Center, Pittsburgh, PA.

Background: Osimertinib, an oral irreversible EGFR tyrosine kinase inhibitor, had promising results in patients with EGFR T790M resistance mutation of non-smallcell 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% in osimertinib group and 75.9% 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 19Del and T790M mutation and EGFR L858R/T790M mutation. Clinical trial information: NCT02959749.
**MET amplification (amp) as a resistance mechanism to osimertinib.**

**First Author:** Zofia Pietrowska, Massachusetts General Hospital Cancer Center, Boston, MA

**Background:** Osimertinib (osis) is an EGFR T790M inhibitor. Mechanisms (meth) 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 (tum) biopsies (bi) underwent NGS (SNPShot, MGH and Foundation Medicine [FM]), MET amp (target: MET copy number > 2.2) and C797S. Plasma underwent cfDNA NGS (Guardant360). Results: Of the 23 osi-resistant EGFR-mutants (13 with MET detected), 10 (43%) had T790M, 21 acquired T790M. 13 had prior 3rd gen EGFR TKIs before osi - osiروب (11), ASP2373 (1), EGFR161 (1). Median time on osi was 12 mos (range 2-25); median total time on 3rd gen EGFR TKIs was 18 mo. Bx types were tissue (16), plasma (18), and both (11, median 31 d). All pts retained their founder EGFR mutation, but 15/23 (65%) had 21/3 (22%). 1 pt had SCLC T790M post-osi, suggesting AR arose from a T790wt subclone (Table). Common AR meth were MET amp (7/23; 30%) and EGFR C797S (5/23; 22%). 1 pt each had SCLC T790M post-osi, suggesting AR arose from a T790wt subclone (Table). All pts retained their founder EGFR mutation, but 15/23 (65%) had 21/3 (22%). 1 pt each had SCLC T790M post-osi, suggesting AR arose from a T790wt subclone (Table).

**Characteristics and outcomes of patients (pts) with metastatic KRAS mutant lung adenocarcinomas:**

**First Author:** Nitin Roper, National Cancer Institute, Bethesda, MD

**Background:** Intratumor heterogeneity has been characterized among multiple cancer types. In lung adenocarcinoma, APOBEC-mutation 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-mutation during metastasis to other sites. We applied whole exome sequencing, RNA-seq, OncoScan CNV and mass spectrometry-based proteomic analyses on 46 tumors. We found that metastatic tumors contain a unique subset of mutations and alterations that are specific to metastasis. In particular, we found that APOBEC-mutation is significantly associated with poor OS in both tumors and plasma. Conclusions: APOBEC-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.

**Rapid/rapid autopsy to reveal APOBEC-mutation 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-mutation 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-mutation during metastasis to other sites. We applied whole exome sequencing, RNA-seq, OncoScan CNV and mass spectrometry-based proteomic analyses on 46 tumors. We found that metastatic tumors contain a unique subset of mutations and alterations that are specific to metastasis. In particular, we found that APOBEC-mutation is significantly associated with poor OS in both tumors and plasma. Conclusions: APOBEC-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.

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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 tumour DNA abnormalities may not be represented or 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. Archived 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-amplillum 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%); TPS3 (45%), KRAS (15%), EGFR (3%), MET (5%) and B R A F v 600 E (32 pts, 12 with V600E), 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 (65pts, 3 with V600E), MET were present with MET exon 14 with M E T L 858 R (10, ERRORS<0.0001), 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 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: Ibiyai Diaggo-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). ≥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, ≥1 GA was detected in 63/78 (82%) 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, GFRF3, PDGFRα) were identified in 5% (39/856) of cases. Diverse and novel mechanisms of acquired resistance (AR) were detected in ctDNA including MET Y1230C and GFRF amplification post-crizotinib, GFRF3-TACC3 fusion post-EGFR inhibitor, and multiple GFRFAR 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.
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 clinico-pathologic 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_Q719delinsF = 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 mutations, 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; IIA = 1; IIIA = 1; IIIB = 2. 34/63 pts with metastatic disease were treated with the following TKIs: erlotinib = 14, afatinib = 5, osimertinib = 1. Median duration on TKI treatment in months was: erlotinib = 10 mo, (range 1-25), afatinib = 5 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 ex19del/EGFR L858R mutations had a median OS of 31 months (95% CI 28-33) (Naidoo Cancer2015). 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) are the 3rd most common EGFR activating mutation, and are generally unresponsive to 1st and 2nd generation EGFR-TKIs. Development of third generation 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_N771insASVD and V769_D770insASV) and pt derived xenograft (PDx) of 3 EGFR Ex20Ins (V769_D770insASV, M661_A767insASV, H773_V774insPHI) 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 AZ2104 (50 mg/kg/day) and osimertinib (25 mg/kg/day) and assessed for tumor growth inhibition (TGI). Immunohistochemical analysis was performed for EGFR and relevant signaling pathways. A pt from whom the V769_D770insASV Ex20Ins PDX was derived was treated on a UC IRB approved protocol with osimertinib at 160 mg PO once-daily (QD). Results: At completion of treatment, QD administration of osimertinib or AZ2104 induced significant TGI in xenografts across the 4 EGFR Ex20Ins tumors (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 intestinal pneumocides that necessitated drug discontinuation. Conclusion: 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 AZ2104 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 the 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 to determine a broad range of factors that may impact on treatment. Results: From a total of 26 patients who were either 1) known T790M positive prescreening T790M testing 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 lung cancer. We had a longer PFS associated with lower p-EGFR, p-ERK, p-Akt, p-Stat3 activity across multiple EGFR Ex20ins that comprising the most common Ex20Ins detected in patients (~50% prevalence); metabolite AZ2104 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.

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 heterogeneity associated with response to TKI therapy. 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 driver mutations. We explored whether the EBC could be used for cfDNA T790M detection. Methods: We recruited 26 patients who were either 1) known T790M positive prescreening T790M testing 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 lung cancer. We had a longer PFS associated with lower p-EGFR, p-ERK, p-Akt, p-Stat3 activity across multiple EGFR Ex20ins that comprising the most common Ex20Ins detected in patients (~50% prevalence); metabolite AZ2104 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.
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 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 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

Arafatinib (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: EGCO 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 rate 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 (5%); paronychia (24%); mucositis (6%); diarrhea (5%); liver dysfunction (3%); hypertension (3%); 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-mutant NSCLCs. Clinical trial information: UM1000014710.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Tolerability and antitumor activity of ASP8273 in TKI-naïve 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 (EGFRmut+) NSCLC. Methods: Subjects with EGFR TKI-naïve adult subjects (≥20 yr) 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, 20.0). In subjects with L858R, ASP8273 300 mg was associated with an ORR of 55% 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 EGFRmut+ NSCLC and demonstrated antitumor activity. Clinical trial information: NCT02500927.

Table on page 458s showing adverse events of ≥5% in the study population, by grade:

**Diarrhea**
- Any Grade 1: 24 (77)
- Grade 2: 12 (39)

**Peripheral neuropathy**
- Any Grade 1: 16 (52)
- Grade 2: 4 (13)

**Nausea**
- Grade 1: 16 (52)
- Grade 2: 9 (29)

**Increased ALT**
- Any Grade 1: 10 (32)
- Grade 2: 3 (10)

**Hypokalemia**
- Any Grade 1: 9 (29)
- Grade 2: 3 (10)

**Decreased appetite**
- Any Grade 1: 12 (39)
- Grade 2: 2 (6)
- Grade 3: 2 (6)

81-100

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
**Background:** Resistance to early generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) 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 can result in tumor responses. 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 pacitaxel-trastuzumab treatment in pts with a sensitizing EGFR mutation who show tumor membrane HER2 expression in a tumor biopsy (immunohistochemistry (IHC) = 1) after progression on EGFR TKI treatment. Results: Sample size of 20 pts was calculated to evaluate the primary objective of ≥30% objective response rate. The study was deemed for a maximum of ≥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 10 months, while the unadjusted median overall survival was 30 months with one ongoing responder. 3 pts experienced grade ≥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, Pacitaxel-trastuzumab induces durable objective tumor responses in EGFR TKI pretreated pts with an activating EGFR mutation and HER2 bypass tracking 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.

**Conclusions:** YES1 amplification is found in 68% of the pre-treatment samples where both, analyses by sequencing of clinical, epidemiological and molecular data and 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 was significantly improved in the presence of the analyzed co-occurring aberrations compared to wild-type MET (ORR, 0.0%; 95% CI, 0.06-0.64 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 = 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. Our findings suggest that 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.

**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 mutagenized transposon and hyperactive piggyBac transposase. Transposon-tagged, afatinib-resistant clones were generated by selective isolation of transfected cells with puromycin and 1μM afatinib. Transposon insertion sites were mapped using a modified TruDIS-type method and piggyBac insertion sites 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 (SKF) 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 SKF TKI dasatinib and to siRNA-mediated knockdown of YES1, and tyrosine phosphorylation of YES1 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 790M-negative (95% CI 1 to 16%) and 1/46 (95% CI 1 to 12%) 790M-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. For genomic screens using transposon mutagenesis and routine clinical NGS of patient samples can identify novel mechanisms of resistance to targeted therapies.
Conclusions: 73%, 35%, and 29%.

22.2 months (13.3-45.7 months). The 1-year, 3-year, and 5-year OS were primary endpoint for success which was PFS greater than 6 months. The median first tracranial metastatic lesions. Limited mediastinal lymph node involvement was 0-2. Oligometastatic disease was defined as a maximum number of

ensure balanced stratification of patients in clinical trials.

Conclusions: In a large population based study of NSCLC, de novo meta-

to ratio 1.228[95% confidence interval 1.134-1.330], p-value, that incorporated gender, ECOG and lines of palliative chemotherapy (hazard shorter overall survival and this remained significant in a multivariate model, in the recurrent cohort (p

61%). The median overall survival in the de novo cohort was 4.7 m vs 6.9 m (ECOG

were more likely to be male (52% vs 47%), have poorer performance status (surgery or radiotherapy) and 802 developed metastases. Patients in the de novo cohort who received platinum based chemotherapy followed by oligometastatic therapy alone. Adverse events of MWA was tolerable. Clinical trial in-

chemotherapy group, respectively.

associated death was observed. Chemotherapy-associated AEs were ob-

pheumothorax, and only 15% needing chest tube insertion. No ablation

5.2 (95 % CI, 4.0 – 13.6) ms, p = 0.003]. Multivariate analyses

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)
mean (SD) 69 (54) 56 (37) 76 (59) 52 (39) 53 (42)

mean (SD) 219 (19) 147 (52) 171 (39) 234 (68) 128 (43)

mean (SD) 613 (67) 410 (32) 108 (10) 645 (00) 349 (71)

mean (SD) 584 (40) 413 (34) 687 (45) 648 (71) 47 (100)

This retrospective analysis used clinical data obtained from a prior

practice and will become more valuable as the database grows over time.

Inpatient stay % 18 26 30 29 16
Inpatient stay costs US$ 7399 6500 9488 8864 3748
mean (SD) 219 (19) 147 (52) 171 (39) 234 (68) 128 (43)

mean (SD) 613 (67) 410 (32) 108 (10) 645 (00) 349 (71)

mean (SD) 584 (40) 413 (34) 687 (45) 648 (71) 47 (100)

Patients with de novo metastatic disease and patients treated with curative intent (surgery or radiotherapy) that developed recurrent, metastatic disease. In-

formation 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 meta-

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.

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.

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 informed: nct01185639.

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 com-

mon 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 com-

monly 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: Carboplatin + pemetrexed (CA), Carboplatin + paclitaxel (CP), Carboplatin + bev-aicuzumab + pemetrexed (CBA), nivolumab (N), and docetaxel (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 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.

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Conclusions: HR (95% CI) = 1.11 (1.00, 1.22).

Impact of prior radiation on survival in metastatic lung cancer ECOG-ACRIN trials.

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 Pleines, Merck & Co., 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 PFS: R = 0.695, 95% CI: 0.446-0.844). STE estimation indicated that trials that show statistically significant treatment effect size of ≥43% ORR or ≥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.
Background: Anlotinib hydrochloride, an oral TKI targeting VEGFR, FGFR, PDGFR and c-Kit, showed promising efficacy in Phase III study. Here, we evaluated the efficacy and safety of anlotinib as third-line treatment for advanced NSCLC, a randomized, double-blind, placebo-controlled, Phase III ALTER-0303 trial (ALTER-0303 Methods: Eligible III/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 superiority 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 were 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.

Efficacy

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PFS, median, months

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ORR (CR+PR+SD, %) & DCR (CR+PR+SD, %)

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Treatment-related AEs (≥2 grade), %

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Clinical features of squamous cell lung cancer with targetable gene alterations in a nationwide genomic screening network in Japan (LC-SCRUM-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 screening 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 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-eight (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 PIK3 pathway (PIK3 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 with 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.PS.2. **First Author:** Ajeet Gajra, State University of New York Upstate Medical University, Syracuse, NY

**Background:** Chemotherapy can benefit pts with advanced NSCLC with poor performance status. The role of nab-P monotherapy in pts with advanced NSCLC and ECOG PS 2 is reported. **Methods:** Observational study, retrospective analysis of the phase IIIB/IV SCRUM-J1 trial. **Results:** 40 pts were treated during the first 4 cycles. Median age was 67.5y, 60.0% were male, 92.5% were white, and 65.0% had nonsquamous histology. In the primary analysis, 940 pts (22.5%) discontinued due to TEAEs during induction. In total, 1640 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 protocol-dose of nab-P was 79.8% and the median nab-P dose intensity was 53.2 mg/m²/week (expected, 66.7 mg/m²/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.

**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 ≥70y in a phase III trial, ABOUND.70+. nab-P/C 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 and metastatic NSCLC were randomized (1:1) nab-P 100 mg/m² d 1, b, 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. **Results:** Key secondary endpoints: PFS, ORR, OS, for which statistical analyses do not control for type I error ($P$-values). **Conclusions:** nab-P/C demonstrated efficacy in a subset of pts with NSCLC ≥70 y in a phase III trial. ABOUND.70+ primarily evaluated elderly patients (pts) with advanced NSCLC. There appears to be a signal of improvement in PFS and ORR – 2P N RB1 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) is present in 71% in a phase I trial of trial. **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 to that in small cell lung cancer (SCLC). **Results:** In this study, RB1 mutation is present in 16% of NSCLC patients and 15% of SCLC patients. RB1 mutation was identified 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 = 3.27) in multivariate analyses after adjusting for traditional risk factors. The patients with RB1 mutations were significantly more frequent in the KRAS/EGFR/ALK type compared to the others. The prognostic significance of these RB1 mutations 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 with distinct clinical features according to the molecular subtypes and genotype-directed therapeutic strategy should be developed for the individual subtypes.

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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™) 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. 40% of patients and 52% of LCNEC with TP53 mutations were present in 87%, RB1™ in 46%, STK11™ in 13% and KEAP1™ in 18% of sequenced LCNECs. RB1 was co-activated with TP53 in 94% of LCNEC; mutually exclusive to STK11™ (100%) but not KEAP1™ (57%). NSCLC-ct or SCLC-ct was specified in 92% of patients and RB1™ 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™ NSCLC-ct treated patients was significantly longer than SCLC-ct (p = 0.044), without pemetrexed (p = 0.018). In patients with RB1™ LCNEC OS/PFS was not significantly different for NSCLC-ct vs. SCLC-ct. Conclusions: In LCNEC with RB1™, NSCLC-ct correlates with a more favorable outcome compared to SCLC-ct. Clinical trial information: NCT04650606. Updated conclusions: TCGA 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-SMOMO 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; 16). 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, ECOC-ACRIN MATCH study (NCT02465066) tests SMO/P641A patients with vismodegib.
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 mutation status. First Author: Lyudmila Batcheva, 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 Phase 1/2 or pivotal Phase 2 (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 Phase 1/2 (NCT01449461) and ALTA (NCT02094573) trials. Results: Of 291 CRZ-resistant ALK+ NSCLC pts enrolled in the Phase 1/2 (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+G1202R+G1269A); 1 PD (T1151R+C1156Y+E1190A+F1174L). Of 67 pts with evaluable plasma at BL, 35 discontinued BRG therapy, of whom 20 had evaluable samples collected at the end of therapy. Resistant mutations were detected at EOT in 75% (15/20) of these 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: BRG activity was demonstrated in pts with complex secondary resistance patterns associated with BRG treatment. 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: Carey J. Langer, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA
Background: The ALTA trial (NCT02094573), an open-label, phase 2, randomized, inclusion, 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 dyspnea score, and 90% of all pts reported a reduction or no change in pain score. Approximately 30% of pts had clinically meaningful reductions in these symptoms. Less than 15% and < 5% of all pts reported a 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.

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Conclusions: achieved in 4 of 4 pts with measurable or evaluable intracranial disease with control (stable disease; -34% and -1% in 2 pts with measurable disease) was (n = 27) brain metastases. On a phase 2 trial of cabozantinib, baseline treated with multikinase inhibitors with activity against RET, there were no 84%, with and without brain metastases, p = 0.53) were noted. In 37 pts targeted therapy strategies should address intracranial disease. Clinical disease at diagnosis. Baseline brain metastases were identified in 27% -rearranged lung cancers had metastatic diagnosis date of metastatic disease was evaluated in pts accrued to a global registry. -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, alecitinib, and ponatinib. On a prospective phase 2 trial (NCT01639508), patients with asymptomatic brain metastases were eligible. Intracranial re- sponse to cabozantinib (REDIST 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 (KIF5B100% 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 therapies should address intracranial disease. Clinical trial information: NCT01639508.

09071 Poster Session (Board #307), 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 investigators between 2009 and 2016, the primary endpoint was investigator assessed overall response rate using RECIST v1.1. Other data collected included types of HER2mutations, duration of afatinib treatment and overall survival. Results: We identified 27 patients with metastatic HER2-mutant lung cancers treated with afatinib, median age 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 (S531P) in exon 8; one exon 17 V650E 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 rates were 29% (n = 8), with 8 patients achieving a partial response (24%) and 8 patients achieving a stable disease (15%); the remaining 11 patients (40%) had disease progression. The most frequent 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.

09072 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 BRAFV600E 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 17,129 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. Median age at diagnosis was 64 years. 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 profiles. 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 TPS3 (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, 14/42 (33%) harbored BRAF V600E alterations. Two cases featured primary exon 19 deletion and 790M mutation. Examples of BRAF fusion driven NSCLC responding to a combination of BRAFand 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 EGFRTK fusion positive NSCLC progressing on anti-EGRF 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.
Background: Treatments targeting critical molecular alterations (EGFR, ALK, and KRAS) in NSCLC are highly effective. Our Pathway (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 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 per-tuzumab + 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 months (range, 0.1–24.1 months). Efficacy in the 5 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 (amplification or mutation) and act as oncogenic drivers. Initial cohorts of the BRF113928 (NCT01336634) trial continues. Additional efficacy data and details regarding molecular alterations will be presented. Clinical trial information: NCT02091141.

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<th>Patients, n</th>
<th>ORR, n (%)</th>
<th>Clinical benefit rate, %</th>
<th>Duration of objective response, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 alterationa</td>
<td>31 (19)</td>
<td>10 (32)</td>
<td>4.4, 4.0–7.8</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>14 (63) (1 CR)</td>
<td>6 (57)</td>
<td>4.4, 1.4–7.3</td>
</tr>
<tr>
<td>BRAF other</td>
<td>7 (0)</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td>Hh</td>
<td>3 (0)</td>
<td>0</td>
<td>1.3</td>
</tr>
</tbody>
</table>

+a indicates response is ongoing. *CR + PR + stable disease > 4 months. 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 BRAFV600E mutation. First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: BRAFV600E mutations occur in 1–2% of pts with NSCLC. We previously reported the efficacy of vemurafenib, a selective BRAFV600E inhibitor, in BRAF mutation-positive non-melanoma tumor (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). The prescribed clinical effectiveness 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, 12% had 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 BRAFV600E mutation, with prolonged PFS in previously untreated pts; median OS was not estimated. 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.

<table>
<thead>
<tr>
<th>Pts, n</th>
<th>Confirmed response, n (%); 95% CI</th>
<th>Stable disease, n (%); 95% CI</th>
<th>Discontinued due to AEs, n (%); 95% CI</th>
<th>Stomatitis, n (%); 95% CI</th>
<th>AEs reported, n (95% CI)</th>
<th>Grade 3–5 AEs, n (95% CI)</th>
<th>Grade 3–5 AEs, %</th>
<th>Median OS, months (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>62</td>
<td>43 (69); 39–50</td>
<td>17 (28); 13–34</td>
<td>2 (3); 1–9</td>
<td>19 (31); 24–32</td>
<td>20 (32); 17–33</td>
<td>2 (3); 1–9</td>
<td>2 (3); 1–9</td>
<td>18.2 (95% CI: 14.3–21.8)</td>
</tr>
</tbody>
</table>

Visit abstracts.ascoc.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: We investigated case reports of nivolumab-induced ILD in patients with nonsmall 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 limiting 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, (14.7%) among them showed fatal outcome, whereas non-DAD pattern showed it in 14/120 (11.7%). Male andpretreatment 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.
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 IIB 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 III 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 Schwartsman, 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 determine the need for additional CTx following PD1i. 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 (25%) 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 SA CTx 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 SACTx. Further investigation of a possible chemosensitization effect by immunotherapy is warranted.

9084  Poster Session (Board #410), Sat, 8:00 AM-11:30 AM
Response to salvage chemotherapy following exposure to immune check- point 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 an ICI. 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). CTx imaging was done within 4 weeks of initiation of salvage chemotherapy following PD1i. Retrospective data were reviewed utilizing the Thoracic GEMINI database. Results: Of 306 PD1i-treated patients registered in the database, 28 met eligibility criteria. Among evaluable patients, 46 were males. Sixty-seven percent of 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% CI: 2.10-2.64) in cases versus 1.93 (95% CI: 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 17% controls. Fifteen (22%) cases had progressive disease versus 6 (40%) controls. Thirty-four (51%) cases had stable disease versus 8 (53%) controls. The odds 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.

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Updated safety and clinical activity of durvalumab monotherapy in previously treated patients with stage IIIIB/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/tolerative 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%). In the overall population, 12 mos OS rate was 47% (95% CI 40–53) and 18 mos 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 showed a manageable safety profile in Stage IIIIB/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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 patients with PD-L1-positive 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 randomized 1:1:1 to pembrolizumab 2 or 10 mg/kg every 3 weeks (Q3W) or docetaxel 75 mg/m² 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 arm. 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 ≥50%, and wild-type EGFR mutation status were associated with better OS among patients treated with pembrolizumab. Clinical trial information: NCT01905657.

**Factors associated with OS in KEYNOTE-010**

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race (Asian vs non-Asian)</td>
<td>0.70 (0.54-0.91)</td>
<td>0.0067</td>
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<tr>
<td>Baseline tumor size (cT2N1M0 vs &gt; T1aN1M0)</td>
<td>0.71 (0.59-0.87)</td>
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<tr>
<td>ECOG performance status (0 vs ≥1)</td>
<td>0.79 (0.65-0.97)</td>
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</tr>
<tr>
<td>Histology (nonsquamous vs squamous)</td>
<td>0.45 (0.33-0.70)</td>
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</tr>
<tr>
<td>Baseline LDH (normal vs elevated)</td>
<td>0.61 (0.49-0.76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PD-L1 status (TPS ≥50% vs 1%-49%)</td>
<td>0.64 (0.52-0.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EGFR mutation status (wild type vs mutant)</td>
<td>0.65 (0.46-0.91)</td>
<td>0.0122</td>
</tr>
</tbody>
</table>

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 chemotherapy can play an immunomodulatory role and induce tumor antigen release, supporting combining chemo with immunotherapy. Atezo is a humanized and IgG1 mAb that blocks interaction with PD1 or B7.1. The GP28328 study supporting combining chemo with immunotherapy. Atezo is a humanized and IgG1 mAb that blocks interaction with PD1 or B7.1. The GP28328 study 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 ≥50%, and wild-type EGFR mutation status were associated with better OS among patients treated with pembrolizumab. Clinical trial information: NCT01905657.

**Characteristics (nonsquamous vs reference)**

<table>
<thead>
<tr>
<th>Pembrolizumab n = 690</th>
<th>HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race (Asian vs non-Asian)</td>
<td>0.63 (0.54-0.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline tumor size (cT2N1M0 vs &gt; T1aN1M0)</td>
<td>0.55 (0.43-0.70)</td>
<td>&lt;0.0001</td>
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<tr>
<td>ECOG performance status (0 vs ≥1)</td>
<td>0.65 (0.54-0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Histology (nonsquamous vs squamous)</td>
<td>0.35 (0.25-0.51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline LDH (normal vs elevated)</td>
<td>0.37 (0.26-0.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PD-L1 status (TPS ≥50% vs 1%-49%)</td>
<td>0.28 (0.20-0.38)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EGFR mutation status (wild type vs mutant)</td>
<td>0.33 (0.24-0.45)</td>
<td>&lt;0.0001</td>
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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 I study, pts with recurrent stage IIIb/IV, chemotheraphy-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; 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%/36%, 36%/42%, 42%/42%) and anemia (16%/16%, 16%/16%, 31%/31%). Three potentially related grade 5 AEs were seen (arm C: pneumonia; arm D: systemic candida; arm E: autoimmune hepatitis). Confirmed ORRs were 36%, 64%, and 66% for Arms C, D (1 CR), and E (5 CR). Median PFS (95% CI) was 7.1 months (4.2-8.3) for C, 8.4 months (4.7-11.1) 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 increasing 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: NCT00209449.

**Cohorts**

<table>
<thead>
<tr>
<th>OS (95% CI)</th>
<th>PFS (95% CI)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm C (N+I)</td>
<td>11.2 (7.8, 15.6)</td>
<td>22% (n=25)</td>
</tr>
<tr>
<td>Arm D (N+I)</td>
<td>11.2 (7.8, 15.6)</td>
<td>22% (n=25)</td>
</tr>
<tr>
<td>Arm E (N+I)</td>
<td>11.2 (7.8, 15.6)</td>
<td>22% (n=26)</td>
</tr>
</tbody>
</table>

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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 Papadimitrikopoulou, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Data from the randomized, phase 2 cohort G of KEYNOTE-021 (NCT02393674) 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 and safety results from 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/m2 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 PAsules 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) 26.6 mo (12.6-32.3) vs 13.7 mo (10.8-16.5); HR 0.41, 95% CI 0.23-0.74, P = 0.0035). 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 nonsquamous 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: NCT02393674.
Deciphering antitumour response and resistance with intratumour heterogeneity (DARWIN II).

Background: The importance of intratumour heterogeneity (ITH) is increasingly recognized as a driver of cancer progression and survival outcome. However, understanding how tumour and 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 neo-antigens 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: BRAFV600E - 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 (WGI). Clinical trial information: NCT02314481.

First Author: Rathi Narayana Pillai, Department of Pulmonary Medicine, Guy’s, King’s, and St. Thomas’ NHS Foundation Trust, London, United Kingdom

Lung Cancer—Non-Small Cell Metastatic

TPS9099 Poster Session (Board #423b), Sat, 8:00 AM-11:30 AM

Daratumumab: A phase III clinical program—1L atezolizumab plus platinum-based chemotherapy in chemo-naive advanced non-squamous NSCLC.

Background: 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 the combination leaves considerable room for improvement. The anti–PD-L1 mAb atezolizumab (atezo) blocks programmed death-ligand 1 and was recently approved for treatment 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 ligitation 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.

First Author: Lin Li, Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

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.

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 DNA seq, multiplex protein expression analysis and proximity ligitation 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.

First Author: Caroline Elizabeth McCoach, University of Colorado School of Medicine, Aurora, CO

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**Lung Cancer—Non-Small Cell Metastatic**

**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, EGOG 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 (cfDNA) has emerged as a specific and sensitive blood-based biomarker and studies have demonstrated cfDNA 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 practice, 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.

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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.
Pancreas

Liver

information: NCT01274338.

randomized pts on the 2 ipi arms showed no difference in RFS. Clinical trial therapy of pts with high-risk melanoma is associated with significantly more levels that have been tested in E1609.

proval for metastatic inoperable melanoma. The toxicity of ipi is dose-de-

therapy for high-risk melanoma, including high-dose interferon-alfa (HDI) and 

In the U.S., 3 regimens have regulatory approval as adjuvant 

Ahmad A. Tarhini, University of Pittsburgh Cancer Institute, Pittsburgh, PA

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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: Pembrol demonstrasted 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 pembrolizumab 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 y (pembro only) or until disease progression, intolerable toxicity, or ptf 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 performed using 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% (38%) 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 for ipi pt who received complete pembro. 9,7 of 10 pts had an irRC-defined complete response. Additional follow-up revealed no new safety signals with pembro treatment.

Conclusion: Pembrol 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 stopping protocol-specified 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 for ipi pt who received complete pembro. 9,7 of 10 pts had an irRC-defined complete response. Additional follow-up revealed no new safety signals with pembro treatment.

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 BRAF-MB trial, D had clinical activity in BRAF V600-mut MBM. D + T has shown superior over D Alone in pts with BRAF V600-mut nm 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 (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 V600–mut MBM, no prior local treatment (Tx); (B) BRAF V600–mut MBM, 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 LDLH > ULN. At data cutoff (28 Nov 2016; median fl, 9.0 mo), in cohort A, investigator-assessed IRR was 58% (IDCR, 78%), ERR was 55% (EDCR, 80%), and ODR was 58% (ODCR, 88%). Median duration of IR, ER, and OR was 6.0 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 fl, preliminary median OS was 10.8 mo (95% D, 8.7-19.6). Efficiency 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 over D alone in pts with BRAF V600-mut MBM was met. Promising IRR and IDCR were seen with D + T, but responses appear less durable than reported for nm without MBMs. No unexpected safety issues were observed. Clinical trial information: NCT02039947.

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Results:

The results of the phase II trial in melanoma are summarized in the table below. A total of 66 patients were enrolled in the study, with a median follow-up of 68 weeks for the T+I arm and 58 weeks for the I arm. The primary endpoint was Best Overall Response Rate (BORR) at 24 weeks. The BORR was significantly higher for the T+I arm compared to the I arm (38.8% vs 18.0%). The 1-year overall survival (OS) rate was 91.0% for the T+I arm and 81.6% for the I arm. There were no treatment-related deaths, and 28% of patients in the T+I arm experienced grade 3 or 4 adverse events (AEs), the majority of which were due to ipilimumab. AEs in the I arm were less frequent.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>T+I (n=29)</th>
<th>I (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BORR (%)</td>
<td>38.8 (38.8)</td>
<td>18.0 (18.0)</td>
</tr>
<tr>
<td>1-year OS (%)</td>
<td>91.0 (91.0)</td>
<td>81.6 (81.6)</td>
</tr>
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</table>

Conclusions:

The study demonstrated the efficacy and safety of the combination treatment of nivolumab and ipilimumab in patients with stage III-IV unresectable or metastatic melanoma. The addition of ipilimumab to nivolumab significantly improved the primary endpoint of BORR and OS. The study also confirmed the safety profile of the combination, with a manageable number of treatment-related AEs.

Acknowledgments:

This research was supported by the National Institutes of Health (NIH) under award numbers CA180886 and CA203947. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

Disclosure:

All authors have declared no conflicts of interest.

References:


For further information, please visit the abstracts.asco.org website.
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, USA, 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 its 644% of the pts at re-challenge. 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 re-challenge was 23 mts (95% CI 19-26 mts). Independent prognostic factors for survival included BRAF mutation, LDH 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 KRAS mutations after systemic treatment, although this was not significant (p = 0.252). This might be due to the closer contact between those 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.

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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 D’Aviz 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 56y, 51% had mutant BRAF, 41% elevated LDH and 65% were ECOG 1-2 at PD1 start. 58% had prior ipilimumab (anti-PD1) and/or BRAFi and 43% prior NMAK 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%) deceased in RN, 2 (2%) after SRS, (22,1%) 7% after PD1. Most pts had SRS 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 toxic effect 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-ontological support in 820 melanoma patients: What are the determinants for the development of distress? First Author: Andrea Forshacher, 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 the demand 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.

Methods: 820 melanoma patients at the outpatient clinic at the Department of Dermatology at the University of Tuebingen were examined for distress in melanoma patients under systemic treatment for metastases.

Results: 406 (49.5%) men and 414 (50.5%) women were included, mean age was 62.35 years (IQR 52-75), and 78% were married. A, but not cohort B. Consistent with this observation, a parsimonious classifier of transcriptional signature at baseline had superior overall response in cohort A, but not cohort B. Consistent with this observation, a parsimonious classifier of transcriptional signature at baseline had superior overall response in cohort A, but not cohort B. Consistent with this observation, a parsimonious classifier of transcriptional signature at baseline had superior overall response in cohort A, but not cohort B. Consistent with this observation, a parsimonious classifier of transcriptional signature at baseline had superior overall response in cohort A, but not cohort B.
Background: Immune checkpoint inhibitor therapy, ICT, achieves durable remissions in 30-50% of patients (pts) with metastatic melanoma (Larkin et al. N Engl J Med 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 (Velizou 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 (MetaPhAn) and functional (HUMAnd) analysis was performed on MSS data. Disease status was assessed by RECIST v1.1 following the discovery cohort, high levels of PD-1/PD-1 interaction score and/or IDO1/HLA-DR co-expression were objectively quantified in pathologist-selected regions using novel Automated Quantitative Analysis (AQUA) algorithms. Responses in over half of pts and some evidence of increased toxicity. Clinical trial information: NCT01543698.

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), Eubacterium limosum (p = 0.04), and Lactobacillus plantarum (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 Gastroenterol 2006). To gain mechanistic insight and confirm causality, short-term metabolomics on the same fecal specimens used for MSS on vivo transmembrane 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-1 interaction score and/or IDO1/HLA-DR were associated with improved response to anti-PD-1 and higher progression-free survival. Identification of a strong interaction score (proportion of PD-1+ cells co-localized with PD-L1) and IDO1/HLA-DR co-expression was associated with improved overall survival compared to single marker assessment. Conclusions: This novel multiplexed multiparametric spatial profiling key immune suppression pathways used for mm trials 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.

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 (lgG4 mAb targeting LAG-3) + nivo (lgG4 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)1173 [F232]). Here we describe preliminary efficacy of BMS-986016 + nivo in pts with MEL whose disease progressed on/after PD-1/PD-L1 and LAG-3 expression and clinical characteristics of responders. 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 (DOR; 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 PD-1/PD-L1 therapy, and 20 (47%) had ≥ 3 prior AEs of any grade. In the 31 efficacy-evaluable pts to date, ORR was 16% (95% CI: 7.6-25.8) and DCR was 46% (95% CI: 32.7-59.3). Five pts (5%) experienced pseudoprogression, and 15 (15%) had ≥ 3 prior AEs of any grade. In patients 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.

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


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 (lgG4 mAb targeting LAG-3) + nivo (lgG4 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)1173 [F232]). 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 (DOR; 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 PD-1/PD-L1 therapy, and 20 (47%) had ≥ 3 prior AEs of any grade. In the 31 efficacy-evaluable pts to date, ORR was 16% (95% CI: 7.6-25.8) and DCR was 46% (95% CI: 32.7-59.3). Five pts (5%) experienced pseudoprogression, and 15 (15%) had ≥ 3 prior AEs of any grade. In patients 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.

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 10 mg/kg Q3W or IPI 3 mg/kg Q2W until progression. Immunopharmacology (eg, PD-1/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 = 125). Conclusions: 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.

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 or IPI 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 select GI AEs. Of 132 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 (IMMs) were used in 61/67 (91%) pts in the NIVO+IPI group and in 41/41 (100%) pts 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 3/4 select GI AEs was 96%, 97%, and 95% with a median time to resolution of 3.9, 3.0, and 3.9 weeks in the IPI group, 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.

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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 that 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 (NCT01256804). 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.

Conclusions: CheckMate 172 is the largest study of NIVO efficacy and safety in pts with MEL who progressed after IPI and confirmed that NIVO had any glucose increase consistent with type 1 diabetes. Efficacy outcomes were encouraging in this difficult-to-treat subgroup of pts with poor prognostic factors, such as uveal melanoma and brain metastases.

Clinical trial information: NCT02156804.

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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 in the PROCLAIM registry. Methods: Data from 112 pts with mRCC were 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 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 and subsequent to chemotherapy (CT), 27 were attributed to IL2 only, and in 13, IREs were due to either IL2 or CT. KC was 73% for IRE group vs 56% for no IRE group (p = 0.0004). OS was significantly greater for IRE group during/after IL2 compared to no IRE/after IL2 in MM, med 46 months (mo) vs 18 mo (p = 0.0004) 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 IL2 during IL2 group and 28 after IL2 group. IL2-related IREs included hypothyroid 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, resulting from IL2 and from CPIs that are qualitatively different and likely reflect different mechanisms of action of immune activation and response. IREs were categorized as: 1) Grade 1/2 responses out of 13 evaluable patients.

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Incidence, patterns of progression and outcomes of melanoma brain metastasis (MBM) during programmed-death 1 inhibitor (PD1I) therapy. First Author: Gustavo Schwartsman, 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 - 4.16; 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 progression during therapy.

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 Hermès, 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 studied, 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 21.1% of patients who 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.

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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 using hybrid-capture, adaptor ligation-based libraries (mean coverage depth > 600X). TMB was calculated from >1.1 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 introns from 28 genes commonly rearranged in cancer. Hybrid-capture, adaptor ligation-genomic profiling was performed in 2,197 MMs for up to 315 cancer-related genes. We assessed base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes. We identified 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 introns from 28 genes commonly rearranged in cancer.

Significant driver GA

BRAF

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<th>Gene</th>
<th>CT</th>
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<td>Mutation</td>
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Conclusion: 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.

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 metastases at diagnosis, of these 11 pts 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 of 2.5 months (95 CI 1.2 – 3.6m).

Conclusion: After BRAF/MEK inhibition, due to rapid disease progression and poor performance status a significant proportion of patients do not receive immunotherapy and for some may have 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.

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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 Knaapen, Department of Clinical Pharmacy and Toxicology, Care And Public Health Research Institute, Maastricht University Medical Centre, 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 hazard ratios (HRs) 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.

Stable disease (SD) in 7 (A), 6 (B), 8 (C) and 6 (D). Adverse events (AEs) were response evaluable pts (and 4 pts with early death) (N = 76) is shown in Table 1. Overall survival (OS) (eligible and treated pts; N = 80: 18 III/M1a, 24 M1b, 38 M1c) were no significant differences in PFS with HDI vs. no HDI or ipi10 vs. ipi3. Response based on the log-rank test for 80 patients (pts) these comparisons would have 82% power to detect a 30% difference in OS (20.8 vs 17.9 mos, 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 V600KR) confirmed these findings. There was a trend toward higher mutational load in V600R/K than V600E, confirmed with TCGA data (p < 0.05). V600K/R had a higher proportion of mutations in PIK3CA and several tumor 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. Further correlative studies are needed to better understand the reasons for the different responses. Given that two melanoma subgroups.

ratin x (A): 0.02, 0.17. (B) 0.01, 0.20. (C) 0.01, 0.20. (D) 0.01, 0.20.

Results: Using TCGA data, confirmed with TCGA data (p < 0.05). Analysis of TCGA data (122 V600E, 21 V600KR) confirmed these findings. There was a trend toward higher mutational load in V600R/K than V600E, confirmed with TCGA data (p < 0.05). V600K/R had a higher proportion of mutations in PIK3CA and several tumor 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. Further correlative studies are needed to better understand the reasons for the different responses. Given that two melanoma subgroups.

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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 panenteritis (3%), with 13% (n = 17) experiencing >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, dematitosis 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 occurred: recurred irAEs: grade 4: 46%, grade 2-3: 33%. grade 1, 13%, grade 4, and 7% of 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.

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 2013 and May 2016, 153 pts were enrolled in a phase I trial of panobinostat with ipilimumab in advanced melanoma. ctDNA was detected at baseline and during the first 12 wks of treatment. Based on our prior studies, ctDNA results were grouped in ‘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 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. ctDNA was detectable at baseline in 23/29 (76%) and at wk 12 in 19/29 (65%) with 5/29 (17%) pts experiencing >1 fold decrease in ctDNA at wk 12. Conclusions: ctDNA in patients with mm at baseline and early on aPD1 treatment differentiates true from pseudoprogression.

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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 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 from the 1st dose of IT. For pts (n = 40; mono and n = 40; combo) who d/c IT for reasons 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/hematologic 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 23 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 or death/are shown in Table. Reasons included CR, toxicity, or other (most commonly protocol completion or prolonged PPI). 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/other 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.

Table

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<tr>
<th>Age (years)</th>
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<tbody>
<tr>
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<th>M1B (%)</th>
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<tr>
<td>Combo (n = 56)</td>
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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 Boutoues, 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, 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 (irRCC). 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, disease-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 = 2) and drug-related colitis (n = 1) (Esosinophilia and systemic syndrome) (n = 1). DLT occurred in 2/6 pts in the cohort receiving 15 Gy. No drug-related death occurred. According to irRCC, 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 at 9 Gy appears to be associated with antitumor activity. Clinical trial information: 2010-020317-93.
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 CR02 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 2d 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 12.9 mths. There was 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: immune-sensitization to radiation (PRE), immuno-radio direct synergy (CO) or radiosensitization to immunotherapy (POST).

9554 Poster Session (Board #162), Sat, 1:15 PM-4:45 PM
The safety and efficacy of high-dose ipilimumab (IPI) and the combination nivolumab plus ipilimumab (NIVO + IPI) in patients (pts) with unresectable 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 III trial of IPI for the tx of high-risk 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 the remainder of the study. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was incidence of 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: transaminisits (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 a leukemoid reaction, and one pt developed diarrea. This was at the 3 mg/kg dose. In the NIVO + IPI cohort, Gr 3 transaminisits & 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: NCT01858194.

9555 Poster Session (Board #163), 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 Edentown, 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 III 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 16.0 months. There was a favorable 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 nformation: NCT01325441.

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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-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 unchargeable or metastatic DM. Available baseline biopsies were analyzed 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-PD-1/L1 at UCLA. Results: At a median follow up of 20 mo, the PD-1/L1-pts (N=57) had similar OS vs the D cohort (HR = 9.95, P= 0.0005). Conclusions: CD8+ T cell infiltration improved for pts with immune GS. PD modeling confirmed the importance of GS as an independent prognostic factor for PD-L1 but not OS. The preferential association of immune GS with favorable prognostic subgroups in the C+V and Y but not D cohorts and known effects of MAPK signaling on immune response further merit exploration in prospective studies.

Impact of gene expression profiles on clinical predictors of survival in patients (pts) with BRAFV600E-mutated metastatic melanoma (mM). First Author: James M. G. Larkin, The Royal Marsden NHS Foundation Trust, London, United Kingdom

Background: Treatment of BRAFV600E-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 Res2015;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 for all pt subsets 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: Immune GS was significantly associated with improved survival vs cell cycle PFS and OS predictors vs V across prognostic subgroups. Immune GS was significantly associated with survival benefit for pts with immune GS. PD modeling confirmed the importance of GS as an independent prognostic factor for PD-L1 but not OS. The preferential association of immune GS with favorable prognostic subgroups in the C+V and Y but not D cohorts and known effects of MAPK signaling on immune response further merit exploration in prospective studies.

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: 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) evaluable by IHC and 63% (45/71) evaluable by PCR, of 66 pts tested by both IHC and PCR, concordance was 90.9%. MCPyV+ and MCPyV- pts had similar response rates of PD-L1+ tumors to avelumab. Avelumab had 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 MCC PARP signaling and anti-tumor activity in MCC may identify novel biomarkers. Clinical trial information: NCT02155647.

Analysis of mutational burden and adaptive immune response in desmoplastic melanomas treated with PD-1/L1 inhibitors. First Author: Siwen Hu-Lieskovski, 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-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 unchargeable or metastatic DM. Available baseline biopsies were analyzed 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-PD-1/L1 at UCLA. Results: At a median follow up of 20 mo, the PD-1/L1-pts (N=57) had similar OS vs the D cohort (HR = 9.95, P= 0.0005). Conclusions: CD8+ T cell infiltration improved for pts with immune GS. PD modeling confirmed the importance of GS as an independent prognostic factor for PD-L1 but not OS. The preferential association of immune GS with favorable prognostic subgroups in the C+V and Y but not D cohorts and known effects of MAPK signaling on immune response further merit exploration in prospective studies.

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Evaluation of the Melanoma Tumor Burden Score (MTBS) in a real-world setting.

**First Author:** Michael Weichertenthaler, 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 (ADORreg) 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 and 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 896 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 recurrence significantly correlated with outcome when adjusted for age, sex, LDH, and number of metastatic sites. Moreover, change in MTBS correlated to a formal response according to RECIST. **Conclusions:** The MTBS appears to be a promising tool for meaningful quantification of metastatic tumor load in metastatic melanoma for real life data collection like in clinical cancer registries.

**Table 1:**

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**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 estimated via Fishers Exact test. Survival analysis was compared between two cohorts. Significance of associations was assessed via Fischers 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), 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 chemoradiotherapy 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.
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 year survival (88%, 83%, 86%), 2 year survival (66%, 57%, 61%), 5 year 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 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.

9571 Poster Session (Board #179), Sat, 1:15 PM-4:45 PM

Multivariate analysis of multiprotein serum predictors at baseline of progression-free survival of ipilimumab or nivolumab and nivolumab in the Checkmate-069 study. First Author: Kristian Homico, 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/PD-1 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 nivolumab/nivolumab (IPI/NIPO). 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 markers with PFS as predictors 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 (760 pg/ml), CCL15 (> 2.7 ng/ml), and TACE (> 600 pg/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, HRlogrank: 0.07, 95% CI: 0.03279 to 0.1533). The same markers did not significantly in responders and non-responders. By RNA sequencing no differential expression profiles between responders and non-responders was found. Conclusions: Our study 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.

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: Marjix Heinen Geukses Poppen, 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 benefiting 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: The 7th PM are currently being finalized. Results: PM 1) Hemoglobin (Hb, g/dL) multivariate analysis (HR 0.97% vs 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 < 0.05). Patients either with 4+ (55%) or 1-3+ (45%) positive CD8 cells had OS of 25.1mo (95%CI 9.5-50.7) and OS of 15.8mo (95%CI 7.0-24.7), respectively. 5 (4%) died with a CD8 score of 2.5mo (95%CI 0-5.7), 1PM 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 15.8mo (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.
88% (21/24) of recurrences. Kaplan-Meier event rates for each class are shown (9/12) were called Class 2. Combined GEP and SLN risk prediction identified (SLN). Median follow-up time was 1.5 years for pts without a recurrence. Of 25 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-negative, consistent with class 1 pts have 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 extant 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). **Results:** 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: NCT02359557, NCT02355587.

### Clinical outcome rates at 1.5 years in prospective cohort.

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p<0.001 for each endpoint

5-year DMFS 5-year MSS

97% 99%

SLN– (n = 71) SLN+ (n = 330)

92% 91%

Class 1 (n = 71) Class 2 (n = 71)

83% 89%

5-year DMFS 5-year MSS

97% 92%

Class 1 SLN+ (n = 41)

80% 92%

Class 1 SLN– (n = 30)

42% 82%

Class 2 SLN+ (n = 330)

24% 30%

First Author: Edy C. Hsueh, Saint Louis University, St. Louis, MO

**Background:** Decision-Dx-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 1.2 mm, 55% were male, 20% (58/293) 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-negative, consistent with class 1 pts have 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 extant 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). **Results:** 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: NCT02359557, NCT02355587.

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Class 2 SLN+ (n = 330)

24% 30%

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 0.2-15.0mm). 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.
Melanoma/Skin Cancers 495s

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 HS 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 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 differential 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 (DEDAS) 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: These 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.

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 = 10) from 39 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 1.1. Significance of MM histology (I/II/III) was explored as a potential predictor of clinical benefit (PD) and toxicity. 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 Ipi/Nivo did not correlate with CD8+ T cell 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 Gardrell, 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 analysis of immune and stromal cell subsets. Methods: I/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, PTEN, B2M, SOXI10, 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 (50X10+) cells when they are proliferating (Ki67+) (p < 0.0001***), while they are closer to MΦ when they are activated (HLA-DR+) (p = 0.0020***). 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 = 0.022) and stroma (p = 0.027) and did not correlate with DSS 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 (ipiv) or nivo). Patients who had undergone surgery prior to 27th January 2017 are included in this preliminary analysis.

A pathological complete response (pCR) is 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 (AJCC: 1B IIIB, 40 IIIC) have completed NAT and undergone surgery. 18 received neoadjuvant immunotherapy (IT): ipiv/nivo x2 doses (N = 10), ipiv/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 22-94). 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.

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**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 role after the adjuvant treatment is not fully defined.

**Methods:** We performed droplet digital polymerase chain reaction to detect BRAF and NRAS mutations in plasma of 161 stage IIB, IIIC/III melanoma patients enrolled in AVAST-M, a randomized study of bevacizumab and ipilimumab versus ipilimumab alone.

**Results:** Twenty pts were identified, nine with stage IIIC and 11 with stage IV melanoma. Seven patients received neoadjuvant vemurafenib (VEM) and two encorafenib. 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/melanocytic (tumoral metastasis), hyalinized, or mixed. 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; these 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 new lesions identified and recurrence was confirmed on MRI HR 2.5, 95% CI 1.3-4.74, p = 0.005.

**Conclusions:** 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. In a retrospective study, we analyzed the clinical and pathological patterns of response in patients with BRAF - V600K 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) and two 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/melanocytic (tumoral metastasis), hyalinized, or mixed. 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; these 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 new lesions identified and recurrence was confirmed on MRI HR 2.5, 95% CI 1.3-4.74, p = 0.005.

**Conclusions:** 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. In a retrospective study, we analyzed the clinical and pathological patterns of response in patients with BRAF - V600K 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) and two 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/melanocytic (tumoral metastasis), hyalinized, or mixed. 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; these 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 new lesions identified and recurrence was confirmed on MRI HR 2.5, 95% CI 1.3-4.74, p = 0.005.
Clonality of T cell repertoire in the tumor (TME) and peripheral blood of 9585 Poster Session (Board #193), Sat, 1:15 PM-4:45 PM

(p = 0.033). The number of tumor-associated clones that were expanded in for trends no significant difference in clonality was seen, but in pts with pCR relapse free (NED) long term vs. those who eventually relapsed. In TME, except was significantly lower at 12 wks (p = 0.025) for pts who continued to be

T cells).

nosequenced in PBMC and TME to determine repertoire clonality and T cell (N = 14) months. T cell receptor beta chain (TCRB) repertoire was immu-

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 immuno-

sequenced 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). T cell fraction 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 = 2.7e^{-7}).

Conclusions: Higher T cell fraction and lower clonality in PBMC when mea-
sured 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: NCT01668594.

Relapse-free survival 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 IIIIB/IIIC), with or without adjuvant therapy, is associated with a high risk of relapse (~70%). We report on a phase I trial of neoadjuvant (neo) + adjuvant treatment with D+T that improves RFS in these pts. Longitudinally collected biospecimens from pts rece-

ing this treatment were analyzed to identify candidate strategies to further improve outcomes.

Methods: A prospective single-institution randomized clinical trial (NCT02403649) of D+T as neoadjuvant (D+T neoadjuvant) or adjuvant (D+T adjuvant) treatment with D+T improves RFS in these pts. Longitudinally collected biospecimens from pts rece-

ing this treatment were analyzed to identify candidate strategies to further improve outcomes.

Methods: A prospective single-institution randomized clinical trial (NCT02403649) of D+T as neoadjuvant (D+T neoadjuvant) or adjuvant (D+T adjuvant) treatment with D+T improves RFS in these pts. Longitudinally collected biospecimens from pts rece-

ing this treatment were analyzed to identify candidate strategies to further improve outcomes.

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 pCR at surgery had significantly improved RFS vs 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.
As of 31 Dec 2016, 4 patients are enrolled in Cohort A; enrollment is correlative studies of immunological effects. Enrollment opened on 05 Aug progression-free survival, and overall survival. Exploratory endpoints include related RECIST measured at Weeks 12 and 18, duration of response, 9 Gy each over 2 weeks. The primary endpoint is safety. Secondary endpoints personalized medicine for acral melanoma patients. compared with cutaneous melanoma patients and sheds lights to the further different driver mutations and distinct transcriptome in acral melanoma patients.

**Background:**

New York, NY

Author: Michael Andrew Postow, Memorial Sloan Kettering Cancer Center, North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC

**Methods:**

We have previously shown that the IL-2 inducible kinase (ITK) is highly expressed in primary melanomas compared with neoVILIBA1-4. Other groups have shown that ITK and BTK are expressed in various melanoma cell lines, various melanoma xenografts and an immunocompetent melanoma mouse model suppresses cell proliferation and retards immunofluorescence (2CIF) that ITK protein expression is increased even in primary melanomas compared with nevi due to promoter

**Results:**

In 111 patients treated with BRAFi and/or MEKi, 212 related cuAEs were identified. The percentage of patients with at least one cuAE is shown in the table below. The most frequent observed cuAE in patients with dabrafenib/trametinib combination therapy were maculopapular exanthemas (18.2%) and erythema-annulare-like eruptions (15.6%), with encorafenib/trametinib combination therapy PPH (10.6%) respectively.

**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.

<table>
<thead>
<tr>
<th>Substance (n)</th>
<th>% of patients with at least one cuAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>encofarifenib (n=26)</td>
<td>73.1</td>
</tr>
<tr>
<td>vemurafenib (n=6)</td>
<td>100</td>
</tr>
<tr>
<td>encofarifenib plus binimetinib (n=48)</td>
<td>31.9</td>
</tr>
<tr>
<td>dabrafenib plus trametinib (n=11)</td>
<td>45.4</td>
</tr>
<tr>
<td>trametinib (n=8)</td>
<td>87.5</td>
</tr>
<tr>
<td>binimetinib (n=25)</td>
<td>92</td>
</tr>
</tbody>
</table>

**Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.**
Pembrolizumab with or without vismodegib in treating metastatic or un-resectable 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 Smo-thampooled 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-L1), suggesting potential potential 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 immunosuppression, 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 version 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.

**Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.**
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 through MEK inhibition with Selumetinib (AZD6244, ARRY-142886) using a continuous dosing schedule improved progression free survival (PFS) in a randomized Phase II study of Selumetinib 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, 4-days-off regimen. An interim analysis is planned after 13 patients have been accrued. Mandatory tumor biopsies will be obtained at baseline, 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.

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 BRAF V600-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 melanoma patients. The objective of this phase II study is to evaluate the clinical activity of the intermittent administration of the combination of vemurafenib and cobimetinib. Patients with advanced melanoma harboring a BRAF V600 mutation will be randomized 1:1 between two treatment groups. Group A will be treated with vemurafenib 960 mg PO BID, Days 1-28, and cobimetinib 60 mg PO QD, Days 1-21 – intermittent – same dosing schedule during first 12 cycles. Group B will be treated 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.

**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, 4-days-off regimen. An interim analysis is planned after 13 patients have been accrued. 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.

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**Background:** Previous clinical trials have shown that vemurafenib significantly increases PFS and OS in untreated BRAF V600-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 melanoma patients. The objective of this phase II study is to evaluate the clinical activity of the intermittent administration of the combination of vemurafenib and cobimetinib. Patients with advanced melanoma harboring a BRAF V600 mutation will be randomized 1:1 between two treatment groups. Group A will be treated with vemurafenib 960 mg PO BID, Days 1-28, and cobimetinib 60 mg PO QD, Days 1-21 – intermittent – same dosing schedule during first 12 cycles. Group B will be treated 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.
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

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

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

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 α=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.  

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30 min</td>
<td>-3.62 (-4.30, -2.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0 to 8 hours</td>
<td>-4.12 (-4.80, -3.43)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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.
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

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 (Standard 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) group (n = 219) or placebo (n = 219) group and received 2,000 mg/day of 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: CRF 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 Relationships 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 adverse events in both groups. Clinical trial information: NCT02039635.

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 aged 65+ yrs 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, patients were referred to GABased recommendations. 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 consultation (43.4%), social worker (26.1%) and geriatrician (22.6%). A total of 7569 actions were undertaken for a total of 572 geriatric recommendations. Recommendations 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 focuses 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.

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 244,766 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 GA to assess older cancer patients with significant comorbidities or functional limitations in 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 cooperators to prioritize self-report strategies to recruit patients that are reflective of their intended population.
Adverse health outcomes in relation 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.

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: NCIORPs 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 (LMMs) included group, time, time2 group, and adjusted for age, education, reading, anxiety, and depression. Results: 589 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) when 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 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 Jeukar, 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 (26%) and 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.

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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 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 > 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 improved survival.

Conclusion: 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.

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**Background:** Chemotherapy may lead to systemic muscle damage. Upregulation of development 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 serum protein levels of MYL5 and MYH8 were assessed pre- and post-intervention from whole blood by qPCR, from serum by Lumexin assays, and from patient-report by the Multidimensional Fatigue Symptom Inventory, respectively. **Results:** T-tests show MYL5, but not MYH8, mRNA levels were significantly upregulated from pre-intervention to post-intervention in exercisers and controls (p < 0.01) with no significant group difference. Additionally, MYL5 and MYH8 serum protein levels significantly increased from pre to post in controls (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 decreases 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.

**Agreement about end-of-life (EOL) care among advanced cancer patients and their caregivers: Associations with care received.**

**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 (53.4%), and palliative care (70.7%). Dyads were more likely to agree about palliative care when patients were female (OR = 1.94, p = 0.03) and ≥ 1.00 Hispanic white (OR = 2.10, p = 0.07) and did not have a college education (OR = 2.04, p = 0.03). 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,ificant group preferences predicted EOL care received. Dyadic agreement about life support was associated with increased odds of patients receiving life support congruent with their preference (OR = 3.02, p = 0.02). **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.
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 cardior pulmonary 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.

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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 patient. 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, 2011 in the Surveillance, Epidemiology and End Results (SEER)-Medicare 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 fu 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 higher overall survival (69% and 54%) vs pts with scores <28 (88% and 73%) (log rank p < .0001). Cox models demonstrated that LWC score and cancer type were significant (LWC: p < .0001, cancer types (compared to B): GI p < .0001, GU p = .013, T: p = .001, M: p = .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, intending appropriate timing for hospice and palliative care consultations, respectively. Conclusions: Pro 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 6mo OS | <29 12mo OS | ≥29 12mo OS | <29 24mo OS | ≥29 24mo OS | <29 36mo OS | ≥29 36mo OS
---|---|---|---|---|---|---|---|---|---
Gastrintestinal (GI) | 331 | 84.7 % | 66.0 % | 60.5 % | 41.0 % | 0.001
Theracic (T) | 143 | 74.6 % | 54.8 % | 52.6 % | 36.0 % | 0.131
Genitourinary (GU) | 140 | 86.6 % | 72.6 % | 68.8 % | 48.6 % | 0.008
Musculoskeletal (M) | 129 | 78.0 % | 64.7 % | 67.6 % | 53.2 % | 0.156
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 uncertain. 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 (ODP) consultation for selected ACP to supplement our usual oncologic care (UOC). 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.

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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-dementia 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 χ² 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 months 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. Havingcriptions 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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-I]) and 2010 – 2015 (Coping with Cancer II [CwC-II]). 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 (US-L), 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-II, LI had higher odds of preferring LEC over 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, 0.9). Within CwC-I, LI had higher odds of preferring LEC compared to LI from CwC-I (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 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.

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 making. Methods: This is a retrospective 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 were fit to receive ST or RT. Results: ST was preferred by the treating physician at therapy initiation in 60% of pts. Within the 10% of pts deemed high risk (CTRS >10; RT required), the 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 H&N (5%) cancer were enrolled. 29 pts received ST (11 had CTRS >10 and 18 had CTRS <10) and 15 pts received RT (10 had CTRS >10 and 5 had CTRS <10). The kappa statistic showed only modest agreement in chemotherapy choice (0.2; 95%CI = 0.01 to 0.45) and no agreement in 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 >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 >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 | >10 (N=10) | 90 | 0.01 | 70 | 0.004
| >10 (N=10) | 35 | 0.33 | 12 | 0.04
| >10 (N=10) | 60 | 0.40 | 40 | 0.21
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 (NCT01137829) 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 comorbidity 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 comorbidity illness reported a functional limitation related to comorbidity. Both the presence of 3 or more total comorbidities (hazard ratio (HR) 1.44, 95% CI 1.08-1.94, P = 0.007) and 2 or more comorbidity conditions (OR 1.95, 95% CI 1.09-3.50, P = 0.02) increased mortality. After adjusting for age, cancer type, and stage, the risk of death increased 12% for each comorbidity condition impacting function (HR 1.12, CI 1.02-1.24), but did not significantly increase for the number of comorbidities. The presence of 3 or more total comorbidities 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. Comorbidity conditions that impair function have a greater impact on survival than the presence of comorbidity alone. Comorbidity assessment should be incorporated into the treatment planning for older adults and can be measured via a simple one-page patient-reported questionnaire.

Immuno-oncology and the elderly: A comparative analysis of participation and toxicities of senior aged adults 65 years and above vs mid age and adolescent/young adult patients on immunotherapy-based phase I clinical trials. First Author: Ishwah Mohan Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Seniors 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 cohorts based on age and collected pt characteristics (sex, age, race, ECOG, comorbidity). We assessed the incidence of ≥1 immune-related adverse events (irAE) in each cohort at end of cycle 3. 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/headneck (n = 84, 20%), GU (n = 54, 13%), and GYN (n = 47, 11%). Median PFS was comparable in all 3 cohorts (2.4 months, 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 AYA and seniors, the incidence of high grade irAE was 35% (95% CI 21-52%) and PFS was 6.5 months (95% CI 5.9-9.0). 58% (n = 23) of pts had G ≥ 3 tox and 30% (n = 12) were hospitalized due to CT. G ≥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 score risk, 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 decrease in PFS of 4.5 months (HR = 1.4, p = 0.01; Log-log, risk score was found in pts that did not require hospitalization (diff = -0.59, 95% CI 1-1.00, 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.
Impacts 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 deafblind) 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 (26% 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.

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. JCO.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 no limitations in ADL or IADL. Participants (n = 111) were randomly assigned to either CARE (n = 56) or usual care (UC, n = 55). 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, 0.2 CARE, p = .121) and participation in SR (.11 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.

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:** 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%); chemoradiotherapy with chemo (4%) 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 0.21-0.7, 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 adenosquamous 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.

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 Jin 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 models, we 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, 0.2 CARE, p = .121) and participation in SR (.11 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.

Multivariable analyses estimating the association between PIM and clinical outcomes.

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>HR/HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>2.81 (HR)</td>
<td>1.36 to 5.81</td>
<td>0.005</td>
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<tr>
<td>DFS</td>
<td>1.49 (HR)</td>
<td>1.09 to 6.62</td>
<td>0.049</td>
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<tr>
<td>Toxicities</td>
<td>2.91 (OR)</td>
<td>1.42 to 5.97</td>
<td>0.004</td>
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PIM. Only 43% of patients received first-line chemotherapy of adequate toxicity (0.0 UC, 2.4 CARE, p = .121) and participation in SR (.11 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.
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 symptoms 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 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 = -32.7, P < .01). Higher depression scores (B = 5.1, P < .01), appetite (B = 3.8, P < .01) and lower energy (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.

Methods: 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 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 = -32.7, P < .01). Higher depression scores (B = 5.1, P < .01), appetite (B = 3.8, P < .01) and lower energy (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.
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 that 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), grip 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 = 0.5-8.8) which normalized at 1-yr (m = 2.5, r = 0.7-3.9; 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 (r = 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.

10046 Poster Session (Board #33), 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. Mumbry, 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. Univariate 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: The SIPAT 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 9.94 (95% Cl. 1.31-26.81) times more likely to die any time after Day 0 – even after controlling for pts’ comorbidity index (p = 0.02). Similarly, compared to G candidates, HR pts were 4.81 (95% Cl. 1.33-16.74) times more likely to die even after controlling for pts’ comorbidity index (p = 0.01). There was no difference between the G and E candidates on univariable (p = 0.75) or multivariable analysis controlling for comorbidity index score (p = 0.72). For every 1 point increase in pts’ adherence score, the risk of death was expected to decline by approximately 14% (HR = 0.86, 95% Cl: 0.78 – 0.96; p = 0.01). SIPAT items that predicted mortality were depressive mood, social depression (p = 0.02), deceptive behavior (p < 0.001) and moderate alcohol abuse (p = 0.001). In linear regression analysis, higher SIPAT score was associated with longer LOS (p = 0.04) but not infection (p = 0.23), GVHD (p = 0.40), or number of hospitalizations (p = 0.73). 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.
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 filled 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 comorbidites, 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.

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: Patient-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; 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 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) and 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 lower cardiovascular 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.
Funded by NCI P01CA163233.

women with years of potential employment ahead, these findings suggest the

Conclusions: Surgical treatment was strongly associated with missing

apy. The vast majority (84%) worked full time at diagnosis, but only 50% had

unilateral mastectomy (8% with reconstruction); 23% had bilateral mas-

20% Latina, 11% Asian), most pts (62%) received lumpectomy; 16% had

benefits were more likely to stop working (OR 1.6) or miss

missing

#

uated correlates of missing

in 2014-15. Of 3672 eligible women, 2502 responded (68%); we analyzed

breast cancer as reported to the SEER registries of Georgia and Los Angeles

Methods:

patients to inform initiatives to reduce the burden of cancer care.

experiences in a contemporary population-based sample of breast cancer

Background:

First Author: Reshma Jagsi, University of Michigan

Massachusetts General Hospital, Boston, MA

foCR. We sought to determine the

likely to be impacted, how FoCR influences emotional distress, and what

dictors of FoCR in this population.

likely to be impacted, how FoCR influences emotional distress, and what

Background:

Contrary to our

Conclusions:

Massachusetts General Hospital, Boston, MA

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-curious 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 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 chemotherapy
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 more problems
managing stress (26% vs. 18%, p < 0.003), and worry more 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 in-
sufficiently 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.

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 Hospi-
tal, 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 random-
ized 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 (Morsky Medication Adherence Scale). Secondary outcomes
were: 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-Satisfaction
scale (FACT-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 MMS adherence (Mean Diff =
5.51, p = .00), and significantly higher satisfaction with care (p = .02).
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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 claims for identification of OP and fractures using HCPCS and ICD9 codes. First, we compared patterns of osteoporosis 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 population. We used data from the National Health Interview Survey (NHIS) and the National Hospital Discharge Survey (NHDS). Finally, we assessed whether absolute estimates of osteoporosis 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 yrs, p = 0.05). 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 population 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).

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.

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 ≥ 80 beats per minute) and abnormal HR recovery (HRR ≤ 12 beats per minute if active cool down, or ≤ 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±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 increased 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 1.07-3.39) and controls (age-adjusted hazard ratio: 4.09 (95% CI 1.09-13.97). Cardiac AD was 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.

Patient and Survivor Care
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: Shilomit Shulov 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 effecter of senescence, in human CD5+ 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 neoAd 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 5 years (NoA) and may have major consequences on the long-term survival of these pts.

10065 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 mnesic 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); 95% 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 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 nodal 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. Further tumor therapy or other clinical parameters had a significant impact on development of CD.
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, gynae, 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 (<1.0 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.

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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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), Folicile-Stimulating Hormone (FSH) and Anti-Müllerian Hormone (AMH) were centrally assessed. CIOF was 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/I vs 5.6IU/I vs 6.4IU/I; E2 101ng/l vs 86ng/l vs 88ng/l; AMH 2.14mg/ml vs 1.58mg/ml vs 0.53mg/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 93.1%, 30yrs 89.7%). 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 (d=dedd, weekly PM(Cb), intense-dd (idd) EnPC) vs conventional dosed CT (PnPC-Eq 3w, 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.

10070 Poster Session (Board #59), Sat, 1:15 PM-4:45 PM
The effect of loneliness on cancer mortality. First Author: Simona Dippolito, Department of Oncology, Santa Maria dei Prati 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 its association to survival rates.

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 age (≤60 vs >60 yrs), stage at diagnosis and clinical (site and stage of cancer, type of chemotherapy, death date), and psychosocial (self-esteem (RSE), perceived social support (MPS2SS), social interaction anxiety (SIAS), personality (EPQR), and depression (BDI)) data.

Results: QLM analyses: loneliness was higher in women than men (F1,398) = 7.5, p = .006) and it linearly increased with age (F1,398) = 10.9, p = .001). Loneliness was also influenced by marital status (F1,396) = 2.9, p = .037), cohabitant of spring (F1,399) = 7, p = .008), and educational level (F1,396) = 4.7, p = .003), but not by clinical variables (all p > .05). Correlation analyses: loneliness was inversely related to RSE (r = -.51), MPS2SS (r = -.52), and extraversion (r = -.32), and directly related to SIAS (r = .46), neuroticism (r = .43), and agreeableness (r = .44). More importantly, a hierarchic regression revealed that patients’ mortality was reliably predicted by gender, stage of cancer at diagnosis, time from diagnosis to UCLA collection, BMI, and UCLA (H(L)8) = 3.53, p = .30). In particular, high BMI predicted higher mortality (Wald = 11.6, p < .001), surprisingly, after controlling for BMI 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 paralling out the impact of, especially, depression. This suggests the role of loneliness on cancer course as an important health concern.
The impact of the Affordable Care Act (ACA) on cancer survivorship.

**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 through 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 access to or coverage of the benefits of the ACA in 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 intended and unintended consequences of ACA provisions on health outcomes and quality of life of this growing population.

**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. 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 disease 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 morbidity trajectory among ovarian cancer survivors is critical to improve their clinical care after cancer diagnosis and allow for increased attention to these potential late effects.

Endocrine and metabolic diseases among colorectal cancer survivors in a population-based cohort. First Author: Maureen 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 with no colorectal cancer diagnosis comprised 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, 95%CI = 2.38, 10.72) and diabetes with complications (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 morbidity trajectory is critical for improved survivorship care.

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. 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 disease 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 morbidity trajectory among ovarian cancer survivors is critical to improve their clinical care after cancer diagnosis and allow for increased attention to these potential late effects.

Endocrine and metabolic diseases among colorectal cancer survivors in a population-based cohort. First Author: Christine Leopold, Harvard Medical School and Harvard Pilgrim Health 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 through 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 access to or coverage of the benefits of the ACA in 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 intended and unintended consequences of ACA provisions on health outcomes and quality of life of this growing population.

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**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 through 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 access to or coverage of the benefits of the ACA in 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 intended and unintended consequences of ACA provisions on health outcomes and quality of life of this growing population.
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, we planned to enroll patients undergoing 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), was measured at the 1st, 2nd, 3rd, 4th, and 5th post-operative clinic visits.

Results: A total of 71 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.

Conclusions: Despite provision of a SBI to patients, SCP 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.
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). Associations 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 and trends of primary care among US cancer survivors, illustrating that CVD 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.
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 -2.6, 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 prophylactically dosed FBT was associated with improved exertional dyspnea, and highlights the need for larger confirmatory trials. Clinical trial information: NCT01856114.

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 Ca (Main) vs. observation (Obs). Upon 1st disease progression (PD1), CAPOX-B or other treatment was reintroduced until 2nd disease progression (PD2). This is the first analysis using scan data of multiple time-points to investigate SMI changes during palliative systemic treatment. Between randomization and surgery, a random selection of 416 CAIRO3 patients (mean age 64.9±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 (obs) at 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 = 0.01), but not with shorter OS (HR 0.94; 0.86-1.02, p = 0.17). 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.

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 definite. 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 Bozuk 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 Bozuk et al along with the ASCO and NCCN 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 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. This accurate, was more difficult to use. The Bozuk calculator, while sensitive, 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 tends to accept but judicious use of CSF.

Risk model | Severe CIN sensitivity | Severe CIN patients not recommended CSF | FN specificity | Pricing for one course of filgrastim ($)
---|---|---|---|---
Hosmer | 89% | 1 | 100 | 44 | 94,705.00
Bozuk | 75% | 2 | 75 | 50 | 80,130.00
ASCN | 67% | 3 | 50 | 50 | 91,062.50
ASCO | 97% | 1 | 100 | 14 | 138,415.00

Impact of scalp cooling using the Scalp Cooling Apleiopeca 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 were planned to receive anthracycline- or taxane- based 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 I 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, 48 (50.5%) patients achieved an average SMI loss was -2.2 units (1.5-2.8) and 63% of patients lost SMI. SMI loss was associated with shorter time to PD2 (HR 0.88; 0.81-0.98, p = 0.01), but not with shorter OS (HR 0.94; 0.86-1.02, p = 0.17). 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: NCT01986140.
Factors influencing the analgesic response over time of the oxycodone-naloxone association in painfull 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 was recorded. All adverse events were classified as moderate-severe, or severe. Results: 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 = 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 were male. None of the investigated polymorphisms influenced the analgesic response at OXN. 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-naive 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 ± 9 years; ECOG 0-1 (%): 98%, NSN 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 incidence/severity of AEs were similar for NEPA and APR/GRAN. Conclusions: This study compared the NK1RA 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.

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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: SWOG 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 evaluable 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 (≥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 and 52. Understanding the mechanism of this persistent effect may inform prevention and treatment strategies. Clinical trial information: NCT00775645.

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 646 chemotherapy-treated ESBC patients (mean age: 51.0 ± 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 contained 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 rs4868371) exceeded the suggestive threshold of P = 1 × 10−5 (Table). Following adjustment for the first two MDS dimensions in the meta-analysis, both SNPs remained as top two SNPs with P < 1 × 10−5. Both rs6443264 and rs4868371 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 function of downstream ESBC cases. The relationship 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 rs4868371 that are suggestive of genome-wide association with CACI among Asian ESBC patients.

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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 ≥ 5% is an established diagnostic criterion for cancer anorexia/cachexia, an analysis was conducted to assess the proportion of patients with ≥ 5% increase in body weight. Methods: NSCLC patients (ROMANA 1 (NCT01387269; N = 484) and ROMANA 2 (NCT01387282; N = 495)) with stage III/IV disease 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 ≥ 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 ≥ 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/m² at baseline (N = 182), 47.3% of anamorelin patients had a weight increase of ≥ 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 ≥ 5% weight gain was applied. The proportion of patients with BMI < 20kg/m² 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.

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 ≥ 5% weight gain was applied. The proportion of patients with BMI < 20kg/m² 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.
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-fluouracil (5-FU)-based CT:** A multinational, randomized, double-blind, placebo-controlled study. First Author: Meinko Hartkau, Hematology and Oncology, Klinikum Neuss-Lennep, 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 FOLFOX) 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, particularly with FOLFOX regimens. Clinical trial information: NCT0209998-39.

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-II 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 PhenOri 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 aromatase gene, 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 and biological 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 phopholipic 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 balm, despite their popular use. We investigated whether a topical nail bed balm containing bioactive polyphenolic rich African salvia officinalis leaves in a natural base of olea europaea, butyrospermum parkii, cera alba and theobroma cacao protected the nail bedsvia 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, sex, number and type of chemotherapy cycles did not differ between the two groups, recruited from 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 Phoraxis Index (NPSI) and a linear severity scale based on clinical examination and photographs. Differences were analyzed using an unpaired t test; significance level α = 0.05 at 95% confidence intervals (CI); probability (p). **Results:** The mean change in nail health outcomes over the treatment period was as follows: $\text{Nail Health Outcome} \quad \text{Baseline} \quad \text{Adverse} \quad \text{Difference} \quad \text{CI} \quad \text{P value}$

<table>
<thead>
<tr>
<th>Nail Health Outcome</th>
<th>Natural balm</th>
<th>Placebo</th>
<th>Difference</th>
<th>CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatology Life Quality (Patient)</td>
<td>0.034</td>
<td>6.1</td>
<td>6.062</td>
<td>4.17 - 7.95</td>
<td>P = 0.00001</td>
</tr>
<tr>
<td>Linear Severity Scale (Patient)</td>
<td>+2.63</td>
<td>-64.1</td>
<td>66.72</td>
<td>52.97 - 80.47</td>
<td>P = 0.00001</td>
</tr>
<tr>
<td>NPSI (Physician)</td>
<td>0.0</td>
<td>-5.71</td>
<td>5.71</td>
<td>4.29 - 7.12</td>
<td>P = 0.00001</td>
</tr>
<tr>
<td>Linear Severity Scale (Physician)</td>
<td>-5.79</td>
<td>-66.1</td>
<td>60.3</td>
<td>45.29 - 75.32</td>
<td>P = 0.00001</td>
</tr>
</tbody>
</table>

**Conclusions:** A double blind, randomized placebo controlled trial evaluating the effect of a polyphenolic rich plant based nail bed balm on the severity of chemotherapy-induced onycholysis. The polyphenolics rich balm or a petroleum balm suitably scented for a placebo control. Demographics, sex, number and type of chemotherapy cycles did not differ between the two groups, recruited from 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 Phoraxis Index (NPSI) and a linear severity scale based on clinical examination and photographs. Differences were analyzed using an unpaired t test; significance level α = 0.05 at 95% confidence intervals (CI); probability (p). **Results:** The mean change in nail health outcomes over the treatment period was as follows: $\text{Nail Health Outcome} \quad \text{Baseline} \quad \text{Adverse} \quad \text{Difference} \quad \text{CI} \quad \text{P value}$

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 NGS data analysis in cancer patients at our institution from 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 collated into a single database. Differences in the timing of NGS ordering near death vs NGS ordering near diagnosis, PC consultation, or death were examined using a Mann-Whitney rank sum test. Results: Analysis included 1596 (807 women) cancer patients. Mean ±SD age was 55 ±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 ±1568.5 days (n = 1546). The difference between date of NGS order and date of death was 221.2 ±186.6 days. Two-hundred and fifty-one patients (15.7%) received their first 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 ±215.6 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 NGS orders. Ordering of NGS in advanced cancer patients may serve as a trigger for PC consultation.

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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: Evtokia 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.

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 treated” plus 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 no 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 and quality with cancer pain. The medication compliance of the intervention group was significantly higher than that of the control group(K2= 46.606, P<0.001), and in intervention group the incidence of breakthrough pain was significantly lower than that of the control group (K2= 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 patient'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 patients (BC) patients receiving docetaxel(D) chemotherapy. Onycholysis, the separation of the nail plate from nail bed, is well 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 group the traditional form of health education and humanization Care model for patients with advanced cancer pain management, can effectively improve patient medication compliance, reduce the cancer breakthrough pain's incidence and quality with cancer pain. The medication compliance of the intervention group was significantly higher than that of the control group(K2= 46.606, P<0.001), and in intervention group the incidence of breakthrough pain was significantly lower than that of the control group (K2= 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 patient's life quality with cancer pain.

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, 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.

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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 5HT3RA, an NK1, and dexamethasone) to prevent chemotherapy-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 antiemetic prophylaxis was or was not in accordance with the ASCO guideline (i.e., Per-guideline vs. Non-Guideline). Rates 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 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 reduced 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-use around 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 de-compression, 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. Analysis was done with 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 comparable between the two arms (p = 0.244). Conclusions: Gastroplegia Patch is safe and effective in treating postoperative gastroplegia in gastrointestinal 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 UROBP 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. (Coch UROBP 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.

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. Matare, 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, clinical 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 ≥ 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%), pancrease (17%) and gastrectomy (17%). Most commonly used regimens included mFOLFOX6 (42%), FOLFIRINOX (23%) and FOLFIROX (12%). Median absolute neutrophil count nadir for all cycles was 453x10^3 (range: 1160-25168). Grade 1 and 2 neutropenia developed in 6 of 536 (1.1%) 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 both effective and safe as next-day administration, benefitting pts and might reduce costs.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 ADT insufficiency (1.25 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 (LSp) 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 (25-28 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’s change: hVITD = −1.5% vs rVITD = −4.1%, p = 0.02, with a trend for the femoral neck (BMD’s change: hVITD = −1.7% vs rVITD = −4.3%, p = 0.06) and trochanter (BMD’s change: hVITD = −1.0% vs rVITD = −2.8%, p = 0.10). There was no difference between groups for LS bone loss (LS BMD’s 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 VITD. 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. BioTech Pharmacal Inc. supplied all agents. Clinical trial information: NCT02064946.

Multimodal therapy for cancer related fatigue in patients with prostate cancer receiving radiotherapy and androgen deprivation therapy. First Author: Siriram 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 (modality therapy, or MMT) on CRF as measured by AUC of Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F) subscale scores in Pt’s 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 2371 vs 2055. 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.
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 $\pm 10$ 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 development of clinically significant, chronic BCRL. These results are lower than reported in contemporary studies and validate recent guidelines supporting prospective screening and intervention for BCRL.

Conclusions: Our study demonstrates that prospective monitoring, CDP, with intervention (OTC sleeve for 4 weeks) triggered by a $\pm 10$-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.
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.” The 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, 4 (2%) felt the referral should occur at the time of analysis, 4 (2%) and 4 (2%) felt there are no further treatment options, and 4 (2%) felt there were 4 (2%) felt there were no further treatments. 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 who felt their 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 timing 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 consultations 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 ≥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, 65% (n = 90) died within 2 months, 20% (n = 45) survived 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 ≥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 results in hospice admission. 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: Oleksiy 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, diabetes, smoking, obesity, HTN, angina, CV disease, dyslipidemia, stroke, myocardial infarction, 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. 199/163 (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:0.74-0.98). A total of 129/163 (79%) pts who experienced SCTx received RT. The majority of SCTx pts reported their referral was “just in time,” 42 (21%) felt it was “late/much too late,” and 14 (7%) felt it was “too early.” The 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, 4 (2%) felt the referral should occur at the time of analysis, 4 (2%) and 4 (2%) felt there are no further treatment options, and 4 (2%) felt there were no further treatments. 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 who felt their 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 timing effect and the small number of patients who felt their referral was late.

10124 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 (CGA) 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 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 stratified treatment approach shall result in patient groups with a stable or improving CGA performance during the 1st cycle of treatment. The hypothesis is that individualized assessment directed treatment algorithms identify elderly pts (70 yrs), who benefit from combined nab-P/gem therapy. The study uses a CGA to stratify pts as GOQ (SLOWGO or FRAIL). Depending on test outcome, pts receive chemotherapy (GOQ: 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 Barthel activities of daily living (ADL),I vs. ADL,II after CGA assessment. Secondary endpoints are CA scores during the course of therapy (CGA-1), 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 algorithm 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 T1c-T3, 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 QLQ30-BR23], EORTC-FA13, 12 Item Short Form Survey [SF12], Global physical activity questionnaire [GPAQ], 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 S01 QUALIORT study (ID-RCB: 2015-A01922-47). First Author: Florence Jou, St. Eloi, Beziers, Caisse G. Francaise

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 ≥2 lines of metastatic chemotherapy, ECOG PS ≤2, controlled pain (VAS ≤3/10), and life expectancy ≥3 months. The phase II part (120 patients) will evaluate the feasibility of a 3-month SPEP using the rate of patients performing ≥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 recommended physical activity and/or improve physical well-being (PWB) dimensions of QoL (evaluated with FACT-G and FACT-F questionnaires). To show a difference of ≥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 Ethnic 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.
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.
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 anthracyclines 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, 95% 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 increased risk for CVD. These findings should inform future treatment and surveillance protocols.

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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 gliomas (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 inhibitor, in children with recurrent/refractory LGG assigned to 6 strata and treated at 25 mg/m²/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, hypoalimenten, elevated AST and rash. Rare grade 3/4 toxicities included elevated CPK, rash, neutopenia, 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.
Expansion of HER2-CAR T cells after lymphodepletion and clinical responses in patients with advanced sarcoma. First Author: Moonahkhi 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 1x10^10/mL 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 lymphodepleting chemotherapy can safely induce the expansion of HER2-CAR T cells. Methods: In a phase I clinical study, NCT00902044, we administered 1x10^10/mL autologous HER2-CAR (with a CD28/CD80 antigen 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 1x10^10 cells/m² 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 < 1000/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 cell counts peaked in 5/6 patients (median 8.9-fold range: 4.1 to 28.93) 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 response (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: Expansion 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.
10512 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. Kerran, 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 the treatment of 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 (6.25 mg/kg p6h) 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 yrs) and 66 (81%) were ≥16 yrs. Most common primary diseases were acute leukemias (65%), Kaplan-Meier estimated survival at day +77 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 54/97 pts (66%). 22 (27%) had AEs assessed as possibly related to DF, mostly (≥2%) pulmonary or mouth hemorrhage (4% each) and hematocytia, nausea, encephalopathy, epistaxis, or hypotension (2% each). Hemorrhagic AEs of any relatedness (≥2%) were pulmonary (6%), epistaxis or mouth (4%), and hematocytia (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. Note is the 6% 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.

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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 [15-44] years from diagnosis), the 15-year cumulative incidence of all-cause (21.9% 1970s vs. 12.8% 1990s; p = 0.03) and cause-specific death (15.2% in 1990s, p = 0.05) 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 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.

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 (P = 0.05) 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 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.

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 (DXRZ) is protective for lower-dose doxorubicin (< 300 mg/m²) cardiotoxicity in childhood cancer, but the effect of dexrazoxane (DZX) administered with higher-dose (HD) doxorubicin (DOXO) is unknown. Methods: We evaluated patients from Children’s Oncology Group trials for localized (PS757A) and metastatic (AOS10121) osteosarcoma (OS) who received HD DOXO (375-600 mg/m²) preceded by DZX (10:1 ratio), methotrexate, and cisplatin; some also received ifosfamide alone or ifosfamide/ etoposide = trabuzumin. Outcome was the 6-month cardiac wall thickness for BSA (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. Intraventricular septal wall thickness (µ = -0.84, [-1.2, -0.48]) and LV mass (µ = -0.73, [-1.06, -0.40]) were significantly smaller for both sexes. For females, these became significantly more abnormal with increasing length of follow-up. Females also showed progressive increases in 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. Intraventricular septal wall thickness (µ = -0.84, [-1.2, -0.48]) and LV mass (µ = -0.73, [-1.06, -0.40]) were significantly smaller 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 a 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.
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 97% of cases and 70% of controls received radiation to the breast, breast doses were higher in cases than controls (61% vs 24% breast dose >10Gy), whereas ovarian doses were lower (7% vs 13% ovary dose >10Gy). 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 >50Gy, 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.

Longitudinal analysis of quality of life in children during treatment for acute lymphoblastic leukemia: A report from the Children’s Oncology Group (COG) ALL0932. 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 long-term QOL of young children. Methods: AR-ALL patients enrolled on COG AALL0932 were offered participation if ≥4 years old at diagnosis with an English-speaking parent. At ~2, 8, 17, 26, and 38 (~5 years post-diagnosis) months after diagnosis, 138 (70%) of the 198 still eligible survivors (without relapse and <62 days post-consolidation) completed the PedsQL4.0 and the Family Assessment Device instruments for each child and their primary caregiver. At ~2, 8, 17, 26, and 38 (boys only) months after diagnosis, parents completed the PedsQL4.0 and the Family Assessment Device instruments for each child and their primary caregiver.

Conclusions: 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 7.0-20.6) 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.
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 antitumor 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, treated. Of 369 pts prescreened, 364 were available for PD-L1 expression analysis; of these, 121 (33.2%) were PD-L1+.

Conclusions: The PK and safety profile of atezolizumab in pediatric and young adult patients was consistent with previously published studies in adults. Preliminary antitumor activity was seen in HL and RT; new lower-risk pediatric patients with relapsed/refractory pediatric 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, 3 mg/kg Q14d (cycle = 28d). After 6 additional patients were enrolled in Cohort A, n = 10, the adult RP2D was identified as 3 mg/kg Q21d x 4 then nivo alone Q14d. In Cohort C tested nivo + ipi at 2 dose levels (DLs): DL1 nivo 1 mg/kg + ipi 1 mg/kg and DL2 nivo 3 mg/kg + ipi 1 mg/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 Q21d. Five evaluable patients enrolled in Cohort CDL2 without DLT; then 12 patients enrolled in Cohort CDL2 with one DLT within the 21d reporting period (Gr 2 creatinine increase), defining the RP2D of nivo 3 mg/kg + ipi 1 mg/kg at the schedule above. In 3 phase II expansion cohorts in cohorts A, B2, B4 and C, pleural effusions occurred in 7 with variable contributions 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 Cl0, Cl1 and Cl2 values were 63.2 ± 15.7 mg/mL, 10.7 ± 1.8 mg/mL 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 RP2D of nivo is 3 mg/kg alone or in combination with ipi 1 mg/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.
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 Hribbts, 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, ARST0331, ARTS0431, ARST0531) accruing previously untreated patients with RMS from 1997 to 2013 yielded 1,035 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, 0.03) and 0.77 (SE, 0.03), 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.

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<td>EFS &gt; SE</td>
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<td>Localized (N=1624)</td>
<td>0.73 ≥ 0.61</td>
<td>Favorable site (N=746)</td>
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<td>Unfavorable site (N=878)</td>
<td>0.65 ≥ 0.62</td>
<td>Unfavorable site (N=410)</td>
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<td>Metastatic (N=229)</td>
<td>0.26 ≥ 0.61</td>
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<td>Branch 1 ≥ 0.61</td>
<td>Metastatic site (N=60)</td>
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<td>Acute leukemia (N=141)</td>
<td>0.11 ≥ 0.03</td>
<td>No bone metastases (N=40)</td>
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<tr>
<td>Acute myeloid leukemia (N=51)</td>
<td>0.11 ≥ 0.03</td>
<td>Bone metastases (N=53)</td>
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All Pts N=1624

- All TEAEs, n (%) 10 (18)
- Gr 3 15 (38)
- Gr 4 2 (5)
- CR (%) 15 (38)
- < 50% blasts 10 (25)
- ≥ 50% blasts 11 (28)
- t(17;19) 10 (25)
- MDR response ≤ 10% 15 (38)
- ≥ 6 weeks 10 (25)
- HCT after CR (%) 19 (49)

‡ (p = 0.711) 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.
Conclusions: (58%) have achieved a rapid early response. No patient has required radiation. Patients achieved a complete response to therapy for a CR = 100%. Eleven infusion reaction to Brentuximab. 17 patients have completed therapy. All 17 intermediate, 4 high. Toxicity = 1 episode of GrIII mucositis, 1 episode of GrIII Total = 19 patients. Median age = 15yr (range 4-23yr). Risk = 2 low, 13

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. Toxcity = 1 episode of GrIII mucositis, 1 episode of GrIII

of Bv-AVD-R for Intermediate Risk or Ifosfamide/Vinorelbine for High Risk. We have successfully deleted toxic alkylator, topoisomerase inhibitor, bleomycin and radiation from this treatment regimen. The EFS/OS to date is 100% and 68%, respectively, on the standard arm of the recent Children's Oncology Group (COG) trial, AAML1031. We also observed a decrease in late toxicity.

We retrospectively reviewed medical records of patients diagnosed with de novo LR-AML and treated per the AAML-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/m² cumulative anthracycline dose vs 442 mg/m² for those treated on AAML1031. There was no decrease in LVEF with a mean change of +2.17% for Aflac-AML patients from therapy completion (p = 0.001). There were no 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±4.4% 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. The Aflac-AML regimen resulted in shorter-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.

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 HSPP90 inhibitor ganetespib (GANET) in combination with irinotecan (IRN) and vincristine (VCR). Methods: Orthotopic xenografts (O-PDXs) were created by injecting luciferase labeled RMS cells in the hindlimb 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 rapidly engrafted into 14 to 17-week-old NOD-SCID IL-2−/− mice. Cycles of induction chemotherapy were given on a clinically relevant schedule. Mice were classified as having progressive disease if tumor volume approached 200 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. The 3-year DFS and OS from end of induction I for Aflac-AML patients were 72.7% and 90.9%, respectively. The Aflac-AML regimen resulted in shorter-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.

Results: Total= 19 patients. Median age = 15yr (range 4-23yr). Risk = 12 intermediate, 4 high. Toxicity = 1 episode of Grade III mucositis, 1 episode of Grade III

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 = 12 intermediate, 4 high. Toxicity = 1 episode of Grade III mucositis, 1 episode of Grade III

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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 = 12 intermediate, 4 high. Toxicity = 1 episode of Grade III mucositis, 1 episode of Grade III
Clinical outcomes of adolescents and young adults (AYA) with advanced solid tumors participating in phase I trials. First Author: Raghav Sundaar, 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 2551 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 trials. 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%), P38KCA (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% grades 3–4). 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 L. Golden, 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 1 and 8 of 21 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 CTC AE. Response was assessed by RECIST. Pharmacokinetics (PK) were obtained during cycle 1. Peripheral blood CD56-positive cells were measured d1 and d8 pre-dose. LM 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 ≥3) included anemia, thrombocytopenia, hypertension, hypokalemia, hyperglycemia, hypophosphatemia. Mean D1 C$_{max}$, t$_{1/2}$ and AUC$_{0-24}$ values were 922 ng/ml, 33 h and 27400 ng·h/ml, respectively. LM CD56 expression was 0 (8%), 1+(4%), 2+(12%), 3+(76%). LM and CD55 antibody PK, and response, will be presented. Conclusions: LM (110 mg/m²) is tolerated in children at the adult RP2D. Clinical trial information: NCT 02452554.

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 with 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 approved SCC – 299 in CA and National Cancer Institute-designated SCC) 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.

Poster session #2, Late-breaking oral abstracts: 12:30–1:30 PM, Sun, 8:30 AM–11:30 AM

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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; Clinic 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 (NCT01669084).

Results: Of 17 pts (5 male, age 3-13 years (9-17 y) enrolled, 1 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 (0.0-9.0 y) 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 y) in pts with PR and 4.8 years (0.6-7.3 y) in pts with SD. Seven of 8 pts with PD subsequently received sunitinib, sorafenib, and cabozantinib. Disease progression occurred as an increase in target (n = 2), non-target/new lesions (n = 5), or CT/CEA (n = 1). Six pts died from disease (2 PR, 2 SD, 2 PD) at 4.5 years (0.7-7.9 y) after vandetanib. Outcomes of children with hereditary MTC sustained PR/SD on vandetanib. However, half ultimately required treatment for toxicity. Dose reductions occurred in 8 pts for grade (gr) 2 weight increase in target (n = 2), non-target/new lesions (n = 5), or CT/CEA (n = 1). Six pts died from disease 2.2 years within 1 year of progression 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 doubling time (DT) of < 2 years was found in 22% with or without vandetanib. Patients with PD who died had a median DT of 0.1 years (0.0-0.2 y). Median follow-up for all pts was 7.9 years (0.9-11.9 y).

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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 who 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/m² was escalated to 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/m²: n = 5; 14 mg/m²: n = 11; 17 mg/m²: n = 7). The most common primary tumors were rhabdomyosarcoma (n = 5), Ewing sarcoma (n = 4), and neuroblastoma (n = 3). 3 Dose-limiting toxicities occurred in cycle 1 at 14 mg/m² (increased alanine aminotransferase: 1; hypertension: 2). All pts had any-grade significant. Exposure was similar to that in adults. LEN 14 mg/m²/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 chemotherapeutic in osteosarcoma (OS) and phase 2 LEN monotherapy (RD 14 mg/m²) parts in DTC and OS are ongoing. Clinical trial information: NCT02432274.

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**Poster Session (Board #303), Sun, 8:00 AM-11:30 AM**

**Phase 1 study of pexidartinib (PLX3397) in children with refractory leukemias and solid tumors including neurofibromatosis type 1 (NF1) related pleomorphic 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 phase pharmacokinetics (PK) of pexidartinib in pts (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 (C1 = 28 days) at DL 1: 400 mg/m²/dose, 2: 500 mg/m²/dose, 3: 600 mg/dose. The MTD was defined as Cmax ≥10% of the dose at 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 amylose, 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: Cmax DL1 2.813 ng/mL (12904), DL2 76,569 ng/mL (25,790), DL3 132,903 ng/mL (40,482). The mean (SD) accumulation ratio C1/DL1 (D15 AUC0-24h/C1 D1 AUC0-24h) 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 C, 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 dose (RP2D) is 800 mg/m² dose once daily. This dose exceeds the adult RP2D of 1000 mg/day. Enrollment on the expansion cohort is ongoing. Clinical trial information: NCT02390752.
Conclusions: in multivariate analysis (95% CI of anti-GD2 antibody: 1.270 to 7.990).

0.05 for each). ASCT was not beneficial (p = 0.3 for ASCT vs no ASCT). For

achieved complete remission (CR) after induction chemotherapy and sur-

with

stage 4 NB progressed to stage 4. Among 35 stage 4 patients, 4

achieved complete remission (CR) after induction chemotherapy and sur-

effect on disease control and survival.

ATRX

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mutations (43%) but not

stage 4 NB. Among 35 stage 4 patients, 4

achieved complete remission (CR) after induction chemotherapy and sur-

stage 4 NB demonstrated a high incidence of

somatic mutations and is only partially chemosensitive. However, 3FB/-

3FB-based anti-GD2 immunotherapy appears to improve long-term sur-

visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 have 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 NTRK, 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.

### Table: Tumor Sample Analyses

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<th>Patient</th>
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<th>Plasma Sample</th>
<th>Matched Control Sample</th>
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<tr>
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**Means ± SD**

### Table: Matched Control Sample Analyses

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**Means ± SD**

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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 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 Curve 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 42.6-96.8) & 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. Multivariable CPH regression identified the ability to undergo transplant (HR 32.4 95%CI 9.3-96.8, p < 0.001) & 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.

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). 105 (0.8%) CCS had SOT after study entry with characteristics and outcomes provided (table). Conclusions: Organ-specific radiation and chemotherapy exposure increases the risk for SOT after childhood cancer. Five-year survival rates after renal and cardiac SOT are favorable.

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Relationhip 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 (0.5-0.5 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/5Survivor) 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.

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*p < 0.001, +p < 0.05

Infection related late mortality in survivors of childhood cancer with asplenia or radiation-induced hypospension: A report from the Childhood Cancer Survivor Study. First Author: Brett Weil, Boston Children’s Hospital, Boston, MA

Background: Asplenia or hypospension can develop in survivors of childhood cancer following splenectomy or radiotherapy 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 23,680 5-29 year survivors (diagnosed 1970-1999, median follow-up 28 years, range 5-44) using cumulative incidence and multivariable exponential 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%). Among 10,295 14-19 year survivors exposed to >20 Gy of LUQ radiotherapy, the cumulative incidence of infection related late mortality was 1.4% (95% CI 0.7-2.2%) at 35 years after diagnosis 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 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 (<10 Gy) increased risk substantially. Accordingly, cancer survivors exposed to LUQ radiotherapy should be counseled at risk for infection related mortality. The cumulative incidence of infection related late mortality managed similarly to asplenic individuals with respect to vaccinations and febrile illnesses.

Multivariate analysis of factors associated with infection related late mortality.

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<thead>
<tr>
<th>Treatment</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>No splenectomy; no RT (Ref.)</td>
<td>1.0</td>
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<tr>
<td>Splenectomy</td>
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</tr>
<tr>
<td>No splenectomy, 10-19 Gy LUQ RT</td>
<td>2.4 (1.1-5.2)</td>
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<tr>
<td>No splenectomy, 10-19 Gy LUQ RT</td>
<td>6.1 (2.5-14.9)</td>
</tr>
<tr>
<td>No splenectomy, 20+ Gy LUQ RT</td>
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*p < 0.001

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 = 1.2-2.9). With increasing 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 (LSAE), 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%), benign 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-density lipoprotein (LDL) cholesterol (≤10 mg/dl vs. ≥10 mg/dl) and high-density (≥52 ±16 mg/dl vs. ≥56 ±18 mg/dl) 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) 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.

<table>
<thead>
<tr>
<th>Vascular Biomarkers and Functional Testing</th>
<th>Survivors</th>
<th>Controls</th>
<th>p-value</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
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<td>hsCRP (ng/mL)</td>
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<td>1.3 (1.0–1.8)</td>
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<td>Fibrinogen (mg/dl)</td>
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<td>182 (163–201)</td>
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<td>Surface VCA-M (%)</td>
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<td>44 (38–51)</td>
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<tr>
<td>LASE (minimum Hg ≥18)</td>
<td>16.9 (15.8–18.0)</td>
<td>18.1 (17.0–19.2)</td>
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<td>SAE (minimum Hg ≥100)</td>
<td>6.9 (6.3–7.5)</td>
<td>8.5 (7.8–9.1)</td>
<td>&lt;0.01</td>
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<tr>
<td>PWV (ms)</td>
<td>7.1 (6.8–7.3)</td>
<td>6.5 (6.2–6.9)</td>
<td>&lt;0.01</td>
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</tr>
</tbody>
</table>

*adjusted for age, race, BMI, smoking, physical activity, education, employment

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
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 Childhood 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.
Pediatric Oncology


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 subgroups 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 terontum. 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.

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 0-2 years who died between 2000 and 2011. The frequency of previously defined end-of-life intensity markers (hospital death, intensive medical interventions, IV chemotherapy, and gastrostomy and tracheostomy tube placement) were calculated and multivariable logistic regression was used to determine predictors of SPPC involvement, and whether either SPPC or 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.

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. 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.
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 1 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 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.

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.

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, -KB, and -KC (encoded by NTRK1, NTRK2, and NTRK3) are important for growth regulation, differentiation and survival of neurons. Translocations involving the NTRK2/3 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.

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 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 in children with cancer. Part B combines LTLD at the MTD/RP2D with MR-HIFU induced mild hyperthermia (MHT) in an expanded cohort. Patients ≤ 21 (Part A) and ≤ 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 ≤ 450 mg/m² 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/m² 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.
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 llb/lls study when compared with doxorubicin. **Trial Design**: Phase ll 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/m² [250 mg/m² dos, equiv.] iv q 3 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). Leiomysarcoma 42.5%, liposarcoma 15%, synovial sarcoma 9%, others 33.5%, L-sarcomas (lipo leiomyo) 57.5%. Median PFS Total Pp. (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= 2.99; p = 0.42 (0.41-0.71). Median PFS L-sarcomas (months): A= 5.32; IC= 2.96; p = 0.007; HR = 0.62 (0.44-0.88). DCR Total Pp (%): 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= 30.3; IC= 20.9; p = 0.028. 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.
Activity of cediranib in alveolar soft part sarcoma (ASPS) confirmed by CASPS (cediranib in ASPS), an international, randomized phase II trial (C2130/A12111B). 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 (NCT01377401) was designed to permit discrimination between the impact of cediranib and the often intrinsically in-dolent nature of the disease. **Methods:** CASPS compared C (30mg od) with placebo (P) in a 2:1 double blind randomisation in patients (pts) aged 16 years with metastatic ASPS progressive in the previous 6 months. Pts were un-blinded at week 24, or at progression if sooner, when on P started C. The primary endpoint of percentage change in the sum of target marker lesions (TM) 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%). The median follow-up population (N = 443) had TM 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 (Cversus 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 12mths 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 navigation: NCT01377401.

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**11004 Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

**11004**

**A phase II trial of regorafenib (REGO) in patients (pts) with advanced Ewing sarcoma and related tumors (EWS) of soft tissue and bone: SARCO24 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 x 21. Dose reductions were employed for toxicity and AE. The primary endpoint was PFS at 8 weeks (PFS@8) employing RECIST 1.1. Sample size of 30 allowed determination of the difference between PFS@8 of 50% vs 25% with alpha = 0.05 and power of 91%. **Results:** 30 pts (median age 32, range 19-65; Mf = 2010; 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 (3) 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: 1.40 mg (3.5 tabs, range 80-160) mgs onv2 wk off. 18/30 pts were without PD at 8 wks. Median PFS: 3.6 mo (95%CI 2.8-3.8 mo). PFS@8 by KM was 73% (95%CI 57-89%). Best responses: PR/SD/PD/not evaluable of 3/18/7, for RECIST RR 10%. Two pts with PR had EWSR1-FLI1 fusion. **Conclusions:** The study met its primary endpoint. REGO toxicity was similar to that seen previously. Enrolment continues in LPS and QGS cohorts, and is being expanded to further support EWS without EWSR1-FLI1 fusion. Study of the existing tumor may elucidate which EWS pts may benefit from REGO. Clinical trial information: NCT02048371.

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**11006 Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

**11006**

**Immune response, safety, and survival impact from CMB305 in NY-ESO-1+ recurrent soft tissue sarcoma (STS). First Author: Neeta Samoia, 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 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 N (3 mg/kg q2W) or N(3 mg/kg q2W) + I(1 mg/kg q3W) (N3+I1), with PR had EWSR1-FLI1 fusion. **Results:** Of 11 SS/MRCL pts tested, 64% pts developed NY-ESO-1 specific T cells 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). In months. Median (95% CI)

<table>
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<td>OS</td>
<td>3.6 mo (95%CI 2.8-3.8 mo)</td>
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<tr>
<td>PFS (8 weeks)</td>
<td>73% (95%CI 57-89%)</td>
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Best responses: PR/SD/PD/not evaluable of 3/18/7, for RECIST RR 10%. Two pts with PR had EWSR1-FLI1 fusion. **Conclusions:** N + I showed acceptable safety and clinical response profile. N3+I1 is 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 occurring 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.

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**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 N (3 mg/kg q2W) or N(3 mg/kg q2W) + I(1 mg/kg q3W) (N3+I1). Treatment continued beyond progressive disease (PD) in 11/12 weeks. 5 confirmed responses in 38 evaluable pts yielded 90% objective response rate. Increased TRAEs were observed in N3+I1. Correlative analyses ongoing: NCT02500797. Support: U10CA180821, U10CA180882, Conquer Cancer Foundation, BMS. Clinical trial information: NCT02500797.

**Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.**
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 biomarkers were tested 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 3 PR out of 10 evaluable pts), 2 PR/10 were seen in DDLPS, 1 PR/10 in SS and 0/10 in LMS. For BS, median follow-up was 12.3 months (ORR 10%; 1 PR/10 pts with 1PR/20 OS, 1A/1/1C 3/12, 0/13 ES). 70 pre-tumor samples were analyzed (11 excluded for insufficiency), with PD-L1+ in 3/70 (4%); all were UPS. Of the 2 evaluable pts, 1 had CR and 1 PR. 2 OS were PD-L1+ in 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 on-going and will be presented at the meeting. Clinical trial information: NCT02301039.

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 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-driver genes. 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, but the clinical relevance of other genomic alterations is unknown.

Results: 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-driver genes. One patient withdrew consent after their first visit and was excluded from further analysis.

Conclusions: Five years 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, but continuation strategies are ongoing and may guide combination on-going and will be presented at the meeting. Clinical trial information: NCT00867113.
ABSTRACT

RETRACTED
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 regression 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 among pts with higher educational attainment who 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 controlling for factors was black racial/ethnic pts were less likely to receive LSS than white pts (OR 0.79; p < .001). This suggests disparities in the receipt of LSS vs Amp, and that further research is needed to identify barriers to receipt of LSS for black pts.

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, using a 46-, 50-gene, or 128-gene CLIA certified multiplex platform. 12 pts had a number of potentially actionable mutations in patients with osteosarcoma. Conclusions: Clinical gene panel sequencing can identify a limited number of potentially actionable mutations in patients with 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, site of primary tumor, 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, extra-osseous extension, and risk variables were correlated with OS. The multivariate model was significant (p = 0.014) and all variables were included in the model. Conclusions: Multivariable 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 metastatic osteosarcoma who underwent definitive surgery. Methods: We identified 128 pts with metastatic osarc 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, site of primary tumor, 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, extra-osseous extension, and risk variables were correlated with OS. The multivariate model was significant (p = 0.014) and all variables were included in the model. Conclusions: Multivariable prognostic nomograms for predicting the 10-year probability of mortality and recurrence. First Author: Haotong Wang, Massachusetts General Hospital, 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 cost-effective strategy at a societal willingness-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 $100,000/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.

### Table

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost ($100,000/QALY)</th>
<th>Incremental Cost ($100,000/QALY)</th>
<th>Incremental Effectiveness</th>
<th>ICER ($100,000/QALY)</th>
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<tr>
<td>WW</td>
<td>12,906</td>
<td>2,715</td>
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<tr>
<td>PET/CT</td>
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</table>

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WW, watchful waiting; CXR, chest x-ray; CCT, chest computed 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, QuimperlesMC, New York, NY, MA

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 distance (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 6.9), 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, or the last 6 months. 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: 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 everolimus (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/m², OR = 1.011, p < 0.0001) and, to a lesser extent, with CUM TH-302 dose (mg/m², OR = 1.081, p = 0.0088), STS subtype and prior radiotherapy. Comparing CIV to BOL DOX, neither OS (median 21.7 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 tumor 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 (BA) 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: Comparing proangiogenic factors (FGF, PIGF, 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 D8. There were no significant differences in baseline characteristics (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 55.3 to 31.7 ng/mL, p < 0.01), and a significant increase in PI GF (from a median of 16.1 to 30.0 pg/mL, p < 0.01). In univariate analysis, factors associated with PFS were: de novo 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 PIGF 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 PI GF in AS patients. We did not identify subgroup of pts benefiting from adding of B to WP. Clinical trial information: NCT01303497.
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 CD68, 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 immunono-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 chemotheraphy-induced changes analysis is ongoing. Results: 56 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-y OS) was 74% (95% CI 64-85). Univariate analysis showed better 5-y OS for: a) good responders (good 89% vs poor 57%, p=0.0001); b) pts with CD8/Tia1 tumor 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-y 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 CD2B/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 microenvironmetn at diagnosis is associated with superior survival for patients with localized osteosarcoma, while PD-L1 expression is associated with poorer survival.

### Table

<table>
<thead>
<tr>
<th>CD68</th>
<th>CD4</th>
<th>CD3</th>
<th>FOXP3</th>
<th>Tia-1</th>
<th>CD68/CD163</th>
<th>Arginase-1</th>
<th>PD-L1 (IC)</th>
<th>PD-L1 (TC)</th>
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**Results:**
- 86% 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 immune markers, and chemotheraphy-induced changes were analyzed.
- A TMA of surgical specimens of the same cases was also assembled, and chemotheraphy-induced changes analysis is ongoing.
- With a median follow-up of 8 years (range 1-13), the 5-year overall survival (5-y OS) was 74% (95% CI 64-85).
- Univariate analysis showed better 5-y OS for:
  - Good responders (good 89% vs poor 57%, p=0.0001)
  - Pts with CD8/Tia1 tumor infiltrates (+ > 81% vs +/- 60% vs - 45%, p=0.002)
  - Pts with normal SAP (normal 85% vs high 44%, p=0.04)
- Multivariate analysis showed poor histologic response (p=0.007) and lack of CD2B/Tia1 infiltration (p=0.02) were independently correlated with poorer survival.
- In the subset of CD8+ patients, poorer 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.
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, SPDYIE1 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 MGMTDNA 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 lower. 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 ODR was 11% in negative and 20% in MGMT positive patients (P = 0.8). 6-mos PFS rate was 59% (38-80 %IC), no difference 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. Sunitinib and sorafenib plus everolimus are the only two second-line targeted therapies recommended 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%-86.6%), 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.

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-confidence somatic nucleotide variants (SNV), small insertions 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 burden (fold change = 4.5, P-value < 0.01) has a role in ES progression and 2) is predictive of 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 lower. 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 ODR was 11% in negative and 20% in MGMT positive patients (P = 0.8). 6-mos PFS rate was 59% (38-80 %IC), no difference 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.

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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 months) for all patients, The PTV of IG-IMRT group received total doses were 60 Gy (range, 56-74Gy), delivered with 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.
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 Arkhid, 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 the TOG-S-0312/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 trial: 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 6 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 - 16.2%, in 3 group - 20%, and in 4 group - 74.6% (p = 0.0072) respectively. In the patients with 5-years adjuvant therapy, diseases progression was not noted. During neoadjuvant therapy disease progression was observed in patients of 2 group - 2 pts and in patients of 3 group - 1 pt.

Conclusions: The optimal approach in patients with primary 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 reinfiltration 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 upront 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 personalized 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 may provide a mechanism to overcome IR. In GIST with FGF signaling, the combination of BGJ398 with MEK-inhibition. In GIST with FGF signaling, the combination of BGJ398 with imatinib 400, II line Imatinib 800 or Sunitinib, evaluated with CT scan or MRI: PET status at progressing disease and pattern of tumor progression to I line imatinib therapy were 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. The standard 3+3 dosing schema was evaluated incorporating imatinib 400mg daily continuously in group 1 - 29 patients with imatinib resistant advanced GIST. A standard 3+3 dosing schema for BGJ398 was performed with the following dose escalation and 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, durable disease control was achieved in 11 out of 16 pts (69%). The 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 evaluated to evaluate the significance of the outcome. The univariate and multivariate Cox proportional hazard regression models 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 analyses, 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. Surgery as first line treatment in patient with mixed type of PD as an independent prognostic factor for OS in advanced GISTs.

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11041 Posterior 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). 

**Background:** A subset of metastatic GIST exhibit very long-term survival after imatinib (IM) introduction. The aim of this study was to analyse the clinicobiological characteristics of GIST pts alive > 10 yrs (ys) 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) ys and median ECOG 0 (0-2) yrs. Primary tumors (T) were all CD117+, and mainly gastric or intestinal (64 & 45 pts), with median size 10 (2-40) cm, CD34+ (82 pts), mets/50 HPF ≤ 5 (n = 36), or ≥ 5 (n > 81). Gerontoe 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 metastases (mets) and identify possible factors associated with long-term survival. 

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11042 Posterior 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 behavior (low vs high risk) acc. to Miettinen&Lasota 2002. 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-CD63, 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:** F0p3+ Tregs, CD163+ M2 macrophages and CD11b+ myeloid cells are significantly higher in TKI resistance or neoadjuvant (viable cells > 30%) tissues compared with neo-adjuvant (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 Posterior 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 discontinuation 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 enzyms and develop involved in Imatinib metabolism on these side effects. 

**Methods:** A total of 154 GIST patients treated with Imatinib were enrolled. 22 SNPs (single nucleotide polymorphisms) in KIT/ PDGFRα/ PDGFRβ/ SHC1/ FLT1/ MAPK1/ EGFR/ CCL5/ CXCL14 were detected using Agena Massarray 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:** Imatinib dose, FLT1 n9951465, MAPK1 n16151, PDGFRβ n55712539 and SHC1 n3766920 were found to be correlated with the incidence of myelosuppression (P = 0.027, 0.009, 0.002, 0.008, < 0.001, respectively), moreover, FLT1 n9554314 was correlated with severe myelosuppression (Grade 0 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 n4796120 and CXCL14 n7716492 were correlated with severe skin rash (Grade 0 vs, 2 vs, 4, OR (95%CI) = 1.304 (0.555,3.1807), 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 functional characterization of these targets were done in multiple KIT-mutant GIST and melanoma cell lines 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 intestinal 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 2.19/502, the mean age was 39 years (range 5-70), 596 DT are found in women, CTNNB1 (4-700). 596 DT are found with a shorter time to RIS development (HR 1.89 [0.69-1.13]; p = 0.420). The location of the lesion 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.

11048 Poster Session (Board #371), Sun, 8:00 AM-11:30 AM
Volume tumor 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 respect median changes of -25%, -39% and -50%. Baseline ERO, CAR, and BME ranged 0-19, 0-34, and 0-15, respectively. Median change for ERO was: 0% ERO worsened in 1 pt, CAR did not change, and BME improved in 4 and worsened in 2. Pain Worst NRS and Worst Stiffness NRS improved in 11 and 9 pts, respectively. Conclusions: TVS demonstrated the greatest pain edema improvement, followed by SSD and then conventional RECIST. All had good concordance with PROs. Clinical trial information: NCT01004861.

Concordance of MRI measures with PROs:

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<th>Measure</th>
<th>Pain improved (%)</th>
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<tr>
<td>SLD improved</td>
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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. Cut-offs for platelet-lymphocyte ratios (PLR, > 180) and lymphocyte-monoocyte 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 (56.8%) pts, which was significantly associated with tumor grade (p = 0.0011), 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 1.55; 95%CI 1.01-2.37; 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 high risk of death within stages II (HR 2.20; 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 may improve survival.
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 multicenter 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, 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/IpDL1 in selected sarcoma subtypes are warranted. Clinical trial information: NCT02406781.

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 (GSP-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 nationwide French sarcoma network (NetSarc) from 2000 to 2016. Inclusion criteria was central pathological review of MPT. End-points were local recurrence-free survival (LRSF), 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 follow-up was 4.8 years (range: 0.2 - 15.8). Survival rates at 5 years were LMS, UPS, Others, and GIST respectively and associated with longer LRFS, not significant in multivariate analysis. Conclusions: Maturity 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).

<table>
<thead>
<tr>
<th>End Point</th>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>p</th>
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<tr>
<td>LRSF</td>
<td>Mastectomy at first SS</td>
<td>Yes</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Margins (mm)</td>
<td>0-2 without SS</td>
<td>0.82</td>
<td>0.62</td>
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<tr>
<td></td>
<td>≥ 3</td>
<td>0.68</td>
<td>0.42</td>
</tr>
<tr>
<td>MFS</td>
<td>≤ 20</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>2.14</td>
<td>0.038</td>
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<tr>
<td>Age (y)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>1.96</td>
<td>0.047</td>
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<tr>
<td>Tumor necrosis</td>
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</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.79</td>
<td>&lt;0.001</td>
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<tr>
<td>Margins (mm)</td>
<td>0-2 without SS</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
<td>0.3</td>
<td>0.005</td>
</tr>
<tr>
<td>OS</td>
<td>Metastatic disease at diagnosis</td>
<td>Yes</td>
<td>5.27</td>
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<tr>
<td></td>
<td>No</td>
<td>1</td>
<td></td>
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<tr>
<td>Metastatic recurrence</td>
<td>Yes</td>
<td>7.29</td>
<td>&lt;0.001</td>
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11054 Poster Session (Board #377), Sun, 8:00 AM-11:30 AM
SYNFRIIZ: 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, labeled with a radioisotope. Methods: We conducted a phase I FIH study including adult pts with advanced, refractory SyS. In part 1, pts received OTSA101 labeled with Ir131 used as radiotracer to assess biodistribution and tumor uptake. In part 2, pts with significant tumor uptake were randomized to receive OTSA101 labeled with 370MBq of Y90 (Arm A) or 111Mibq Y90 (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 Y90OTSA101 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 Y90OTSA101, 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 radiomunotherapy targeting FZD10 is feasible and safe in SyS pts. Tumor uptake was heterogeneous but sufficient to select 50% of pts for Y90OTSA101 treatment. Due to limited sample size, further clinical investigations are needed to assess the therapeutic activity of Y90OTSA101 with a recommended dose of 111Mibq of Y90. Clinical trial information: NCT01469975.

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 dacarbazine 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 T 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. Results were 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 56.5 years (range: 31-69). Three pts (16%) 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: 1.4-24). AE with grade 3 and more 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 2 of them had CR for more than 2 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 ≥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 ≥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 fatigue (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 alone or 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: Minnal 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 tazometastat (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 ≥32 wks. Success at stage 2 required DCR in ≥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 ≥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 AE 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). Genomic analysis was performed using whole exome (WES, 5% variant allele frequency) and mutational signature analysis. 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 ≥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 fatigue (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 alone or in combination may be warranted in SS. Clinical trial information: NCT02601950.

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). Trabectedin is usually administered for liposarcoma patients (range 1-63), and 15 months for leiomyosarcoma patients (range 1-35). Disease status at diagnosis was: 44% localized; 56% metastatic. The median overall survival was 17 yrs (2-51). Four patients (pts) received immuno-therapy 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 (≥1) was seen in 50% and 17%, respectively. 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.
11061 Poster Session (Board #384), Sun, 8:00 AM-11:30 AM
Trabeculin and radiotherapy in soft-tissue sarcoma (TRASTS) study: An international, prospective, phase II/III 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 special 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 (1.8 Gy/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) was defined as grade ≥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 (MF 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 transaminists) occurred at Level 1 and another (sepsis due to catheter infection) at Level 2. Overall, grade 3/4 AEs were: ALT elevation (n = 6, 43%), and GGT elevation, neutropenia, anemia, epitelithis 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 < 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 EM 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%) naïve; 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), DM-free survival. 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 (66%); 4 pts were untreated, 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 2/3 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 tumor DNA (ctDNA) named liquid biopsy, has emerged as a new 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). ddPCR for CTNNB1 CMs: T41A, S45P, S45F; and their respective CTNNB1 wild-type probe were designed for ddPCR. Furthermore, we analyzed the correlation of ctDNA levels (CTNNB1 wt/ml plasma) and evolution of the tumor. Results: Initial DT CM status was 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 copies/ml predicted DT progression with a sensitivity of 100% (CI95%: 59-100) and a specificity of 76.5% (CI95%: 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 histopathological 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 retroactive analysis of all patients referred to us with diagnosis of STS in the last 12 months (January 2016 to 2017). According to our 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 clinical-radiological inputs to pathologists. For patients with CTNNB1 wild-type tumors, 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 died and could not retrieve biopsy report. A threshold of 875 copies/ml predicted DT progression with a sensitivity of 100% (CI95%: 59-100) and a specificity of 76.5% (CI95%: 50.1-93.2). Absolute cfDNA quantity was also higher in patients harboring multiple desmoids (p = 0.0292 - MW). Of 97 patients (biopsy = 84, FNAC = 13) who had diagnosis from outside, 37% outside and had discordant report, we divided them into major discrepancy and 24% had minor discrepancy compared with our diagnosis of STS. Of 52 patients, 42 had major discrepancy and 10% had minor discrepancy. Of 20 patients referred from outside was discordant with respect to diagnosis of our centre had major implications on 37%. We believe this is due to lack of sarcoma pathologists and experts with virtually non-existent multidisciplinary clinics in set up outside tertiary care centres.

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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 a series of 255 sarcoma patients in localized phase using the Agilent 014850 platform. Data are available online (http://agsarc.sarcomabbbc.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 un- and multivariate analysis using SPSS 19.0. Results: Expression levels (ELs) of PDGFD and PDGFRD varied across histotypes. PDGFD levels were highest in SyS and lowest in MLPS (p < 0.0001). PDGFD and L ELs were lower in GIST (p < 0.0001), while PDGFD ELs were similar across histological subtypes. PDGFD ELs were highest in MLPS, while PDGFRB L ELs were lowest in GIST and SyS (p < 0.0001 all). Complex patterns of correlation between the ligation and receptors were observed in all individual subtypes. PDGFD 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 the GIST sarcoma cohort (histology, grade, depth, with size, PDGFD, PDGFD as continuous variables): histology, size, grade and PDGFD ELs were independent adverse prognostic factors (PF), while PDGFD ELs was a favorable PF for MFS. In the GIST cohort, testing AFIP score, PDGFD & D ELs as continuous variable, PDGFD ELs was also an independent favorable PF for MFS, in addition to AFIP score. Conclusions: The expression of PDGFD and the accepting receptors varies across sarcoma histological subtypes. PDGFD and D expression levels correlate independently to the risk of metastatic relapse.

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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-monthly following surgery; suboptimal surveillance was defined as CT/ MRI imaging performed less frequently than 6-monthly. 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% (n = 25) in the no surveillance arms respectively. Comparing the 3 strategies, the proportion of pts who then went on to receive curative resection/ metastasectomy 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.

GEISTRA Score versus Clinical benefit and TTP 571

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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 regimens 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) (brotysid and spindle cell/locking). 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 (6A, 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 optimal regimen for adult patients with RMS.

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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: TGCTs is a proliferative, neoplastic joint disease that presents as single or multiple node (local) or multiple nodules (diffuse D-TGCT). Localized over-expression 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 I/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 ≥ 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. 4mg/kg was chosen for Ph2 based on efficacy, tolerability, and PK. AEIs: 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 ≥ 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 myocardiitis. AEIs of CK, 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.

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**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 being 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.

**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 (PFR12) versus historical controls. The design has power of 85% to show improvement in PFR12 from 20% (inactive) to 40% (active) with a = 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.

**Background:** TAPPAS is a randomized phase 3 trial of TRC105 and pazopanib in well-differentiated/dedifferentiated liposarcoma. First Author: Matthew Ingham, New York-Presbyterian Hospital, Columbia University School of Medicine, New York, NY

**Methods:** TAPPAS is a randomized two-stage trial of TRC105/P vs P alone. The first stage enrolled 100 patients with cutaneous disease only, followed until 110 events were observed. The second stage enrolled 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 Data Monitoring Committee 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.

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Filtration assay and CAMLs enumerated, as previously described. Patients were breast (n = 57), esophageal (n = 21), prostate (n = 43), pancreatic (n = 59), the relationship of CAMLs and overall survival (OS) in 6 solid tumor types. The subtypes. However, while their biological association to cancer is being described circulating stromal cell subtype commonly found in the peripheral Cancer Associated Macrophage-Like cells (CAMLs) are a recently MicroTech, Inc., Monmouth Junction, NJ Cancer-associated macrophage-like cells as prognostic indicators of overall survival. 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 systematically studied. Methods: We delineated the landscapes in the T cell receptor (TCR) repertoire, immune infiltration (immunohistochemistry using multiple immune markers), genome (exome sequencing), epigenome (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 evercurrent 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.

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 CDB 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 (13.90 vs 4.79%, p < 0.001). Though no statistically significant differences in CDB 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 = 0.016) 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 TIL 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.

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 with CellSave 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 III), 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 = 0.003). 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 larger CAMLs 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.
Increased CD73 and reduced IFNG signature expression in relation to response rates to anti-PD-L1 (1L) therapies in EGFR-mutant NSCLC. First Author: Katie Streicher, MedImmune, Translational Medicine (currently with EMD Serono), Gaithersburg, MD

Methods: Anti-PD-L1 (1L) 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 0.001-100μM; EGFR was used at 50 ng/ml. CP1108 with NCT01696592 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 TGCA 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). EGFR 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 cell lines, suggesting a causal relationship between the EGFR pathway and CD73 expression. Consistent with these observations, EGFR mutant tumors had ≥2 fold increased expression of CD73 compared to wt (p < 0.05) in TCGA and CP1108 NSCLC adenocarcinoma patients. These EGFR mutations had significantly higher levels of IFNG signature than non-EGFR mutated tumors 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-L1 (1L) in this subset of NSCLC, and suggest evaluating anti-CD73 in combination with EGFR TKis or anti-PD-L1 in EGFR-mt NSCLC.

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 might serve as a predictive marker in pts with mCRC treated with FOLFIRI/bev. SNPs were analyzed by PCR-based direct sequencing. Results: patients (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 R11 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.

EGFR-mt NSCLC.

Methods: We conducted a case-control study to prospectively determine the negative predictive impact of HER-2 amplification or mutations (mut), MET amplification, NTRK/Ros/CCDC6/RET rearrangements, and mut activating MAPKs or NTRK/ROS1/ALK/RET mutations. Patients with RAS and BRAFv600E 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 power of 80% and a 0.05 level of significance. Since hypermutated tumors may hardly rely on a single mut at low allele fraction ** by Hotspot Cancer Panel v2, (Life Technologies), co-amplification was found; ** by Hotspot Cancer Panel v2, (Life Technologies), New BCR-ABL1 in 2(1.2%) cases and 1 (2.1%) control (p=0.001). Msi-high was significantly more frequent among resistant than sensitive tumors (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.

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Genomic analysis of circulating tumor DNA in 442 patients with carcinoma of unknown primary: Implications for targeted therapeutics. First Author: Shumei Kato, Moooi 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: Eighty percent of patients (353/442) had ctDNA alterations with 66% (290/442) harboring at least one characterized mutation. TPF3-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 in the basis of patients (353/442) 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 immunotherapy chosen on the basis of ctDNA findings. The current report suggests that non-invasive liquid biopsies merit investigation in next generation clinical trials.

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 biopsy for HPV6, 11, 16, and 18, and assessment of tumor mutation burden and microsatellite instability. Results: Sites of origin were head and neck (HNSCC, n = 1300), esophageal (n = 242), lung (ISC, n = 2386), and cutaneous (SCC, n = 289) SCC cases. For HNSCC, cSCC, and aSCC (collectively termed HCA SCC), AvC (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 P53-CA (34.9%, versus 16.0%), CYLD (11.4% versus 1.4%) and PTV-CA (29.9% versus 6.1%) for HPV+ cases, and TP53 (38.8% versus 76.5%), CDKN2A (14.1% versus 49.8%), and TERT (14.3% versus 33.0%) for HPV- cases. Mean TM for HPV- and HPV+ cases were 6.6 (STEAD 7.3) and 13.7 (STEAD 29.7), respectively. TMB of all SCC cases was significantly different (p < 10^-12) when stratified by HPV status. For ISCC and eSCC, the most common GA were in TP53 (85.5%), CDKN2A (40%), and PIK3CA (26%) and mean TM was 11.6 with HPV found in 3.1% of cases. In SCC, 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 b Allele deletion of SMARCB1 (~0.3%), amplification of PD-L1 (~2%), and various kinase fusion. 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 site of origin, and have a significantly lower median TMB than HPV negative SCC. Early consistency of responses to matched therapies may strengthen the case for site independent genomic predictors of therapy response.
Whole exon analysis of patients (pts) with metastatic GIST (mGIST) demonstrating exceptional survival with imatinib (IM) therapy compared to those with short term benefit. First Author: Etian 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 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 (9 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 splicing, 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 KITC7 (4 pts), HIF2A (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.
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 a somatic nonsynonymous missense mutations sequenced with a 592-gene panel. High TML was set at ≥ 17 mutations per megabase (mt/MB) based on an established concordance (r=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 = 0.002), and NSCLC (p = 0.022). Higher TML was seen in males than in females in 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 higher TML than in non-mutations.

Table 1: Distribution of TML across different cancer types.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Mean TML</th>
<th>High TML %</th>
<th>TML ≥ 17 &amp; &lt; 30 %</th>
<th>TML ≥ 30 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mel</td>
<td>21</td>
<td>34</td>
<td>56</td>
<td>96</td>
</tr>
<tr>
<td>NSCLC</td>
<td>11</td>
<td>24</td>
<td>46</td>
<td>84</td>
</tr>
<tr>
<td>CRC</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Mel</td>
<td>21</td>
<td>34</td>
<td>56</td>
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<tr>
<td>BLC</td>
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<td>84</td>
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<tr>
<td>CRC</td>
<td>10</td>
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<td>CRC</td>
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</table>

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.

15119 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 18F-FDG PET after a single dose of cetuximab to predict for treatment benefit, PFS, and OS in patients with adenocarcinoma of colorectal origin who are not evaluable for 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/m2 cetuximab every 2 weeks. Before the first dose and before the second dose, patients underwent 18F-FDG PET (FDG PET). PET scans were quantitatively assessed by manual tumor delineation of ≥ 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 ≥ 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 infarction 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 11% 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 of treatment benefit in 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.

15120 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 pathologic response to neoadjuvant chemotherapy (NAC) in a multisite, multiparametric 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 24 were randomized to AC alone. Post-treatment in responders compared to non-responders for non-small cell lung cancer on immunotherapy. First Author: Yashishar Dal Vetel, 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. Intheirprimarycohort(N=25),thefeatureswererankedbasedonthe 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.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: VEGF inhibitor (VEGF) 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 FOLFOX/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 Kimm. Cluster analysis of Tie2 concentration-time course curves showed that pTie2 reflected tumor Kimm 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 Kimm 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 values the vascular compartment as a target. This work identifies the first assay that could optimise use of VEGFi. Clinical trial information: 2009-011377-33.
11525 Poster Session (Board #225), Sat, 1:15 PM-4:45 PM
CD6+ T cells in PBMC to predict the outcome of anti-PD-1 therapy. First Author: Hiroshi Kagaumi, 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 

\[\text{low}\] ) T cell 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 = 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 CD62L 

\[\text{low}\] T cell balance between primed effector and regulatory T cells. Further characterization of CD62L 

\[\text{low}\] CD4+ T cells including mRNA microarray, checkpoint molecules, and chemokine receptors is ongoing.

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 mutations 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) > 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 naïve. 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 = 0.47, p = 0.0002). Mutated genes were consistent with clonal hematopoiesis, with the most frequently mutated genes being DNMT3A, TET2, PPMT1D, 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.
PD-L1 expression in gastric cancer (GC) patients.

Methods: Serial plasma samples were collected from pts with advanced EGFR+ NSCLC and T790M+ acquired resistance treated with osimertinib.

Results: PD-L1 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 CD8 mRNA and low CD8 mRNA levels had significantly poorer overall survival (OS) than those with high PD-1, low PD-1 and high CD8 mRNA levels, respectively (P = 0.05, P < 0.05 and P < 0.05). Multivariate analysis showed that PD-1 low/PD-1 high mRNA levels was independent risk factors for OS (HR 2.15, 95% CI 1.29-3.45, P < 0.01). Flow cytometric analysis of CD3 (T cell marker)-positive cells in the PD-1-positive fraction were 95.4 ± 6.9% in GC patients. Thus, most PD-1 protein expression occurred on T cells. Taken together, PD-1, PD-L1 and CD8 mRNA levels in PB were inversely proportion to 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 gastric tumor immune response and PD-1 low/PD-1 high mRNA levels in PB are markers of poor prognosis in GC patients.

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 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 ARVs. Notably, AR-V7 was most frequently detected, however AR-V3 was detected in 12.3% (95% CI 1.42-14.41; 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.
We then assessed correlations between CTCs (baseline, end treatment, and 4 to 12 weeks post RT. CTCs were quantified using the Oncosensor platform. (7 ml) was collected prior to starting, first week, mid-point, end RT, and every radiation or surgery. Concurrent chemotherapy was allowed. Peripheral blood with oligometastatic cancer undergoing potentially curative therapy.

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 12 to 2 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 1.7 to 5 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.

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 cancer undergoing potentially curative therapy.

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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: Increased ctDNA TMB was derived and was significantly associated with a 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: CP1109/ 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, age, sex, and smoking status. Results: Complete and partial responders (CR/PRs) showed a significant decrease (Δ = -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 (Δ = +2.7%, p = 0.31). This correlation was also observed compared to an increase in mean VAF (Δ = +2.4%, p = 0.033) compared to PD pts (Δ = +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 VAF in pts 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 #230), 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 1~2 SLNs involvement as in Z0011 and AMAROS trials are suitable candidates for non-sentinel lymph node (nSLN) dissection (ALND). But the risk of non-sentinel lymphnode (nSLN) involvement in those early stage patients is still unclear and it is difficult to predict the risk before surgery. Our previous study showed CK19 mRNA in peripheral blood had predicative value of nSLN involvement. A contrast-enhanced ultrasound (CEUS) is a new effective method examining 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 III/IV) and enrolled 12 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 of axillary lymph nodes 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%, 80.87% 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 likelihood = 84.607). The area under curve (AUC) of ROC was significant correlation (r = 0.51, p < 0.05) 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 avoid axillary lymph node dissection (ALND). But the risk of non-sentinel lymphnode (nSLN) involvement in those early stage patients is still unclear and it is difficult to predict the risk before surgery. Our previous study showed CK19 mRNA in peripheral blood had predicative value of nSLN involvement. A contrast-enhanced ultrasound (CEUS) is a new effective method examining 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 III/IV) and enrolled 12 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%, 80.87% 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 likelihood = 84.607). The area under curve (AUC) of ROC was significant correlation (r = 0.51, p < 0.05) 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.

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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-L1-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 (mean, 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 50% or more. No correlation was observed 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.

Dynamics of soluble programmed death-ligand 1 (soluble PDL1) during chemotherapy and its prognostic implication in cancer patients. First Author: Hyeirim 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 a 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 low pre-chemo sPDL1 (≤ 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; 1.23-3.9, 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 correlated with pre-chemotherapy sPDL1 expression and 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.
**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/β-catenin pathway that is activated in almost all types 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 test 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 2,025 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.
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 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 biomarker of LM progression and should be further investigated.

Clinical trial information: NCT01325207.

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. Raza, 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, allelic-fractions of mutations, PD-L1 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. DNA 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 (NHWW) 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 underwnt 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 = 0.702, p = 0.0001). NSCLC group: 71% (16/22) were NHWW 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 DNA/RNA levels. PD-L1 expression was seen in 7/10 pts. Among NSCLC pts, there was a 90% (17/19) agreement in response and levels of DNA/RNA. These were correlated with one another (r = 0.623, 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 and 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. cfDNA is as effective as cDNA as predictive tool for response. Plasma PD-L1 expression is a new tool to monitor immunotherapy response.

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Tumor Biology

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 using 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 ≥20%) in distant-recurrence free survival. We used the CIBERSORT platform to evaluate the immune cells composition according to the expression of CCL5 (higher versus 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 (p = 0.347, P = 0.003). In univariate analysis, TILs (HR = 0.276, 95%CI: 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: 0.150-0.755), in contrast to CCL5 (HR = 0.573; 95%CI: 0.285-1.154; P = 0.14). 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), acivated CD4 memory T cells (4% vs. 2%, P < 0.001; 5% vs. 0%, P < 0.001; 13% 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 enriched CD4 memory T cells and Macrophages M1. Role of these cells in TNBC should be explored more deeply.

11555 Poster Session (Board #255), Sat, 1:15 PM-4:45 PM
First Author: Yinan 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 was 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 tumors, and delay time for tumor killing. Potential predictive factors for tumor growth and killing were estimated and assessed in a multivariate setting. The model was used to simulate response rates at different tumor PD-L1 expression cutoffs. Results: Tumor kinetic modeling accurately describes the longitudinal tumor response profiles from NSCLC patients in both studies. The factors associated with more rapid tumor growth were liver metastases, ECOCG 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% cutoffs, respectively), patients receiving durvalumab (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.

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 tumor infiltrating lymphocytes (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 from 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 ≥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 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.

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 housekeeping genes) was correlated with the variable covariates: age, gender, smoking status, tumor size and histology. The survival (DMFS) was calculated for 33 never-smokers, 75% lung adenocarcinoma. Results: Low expression of FAS-L (p = 0.048), TIGIT and LAG3 was correlated with shorter distant metastasis free survival (DMFS) (p < 0.04). Expression of PD-L1 (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 CX3CR3 was lower in relapsed NSCLC (p = 0.008), the expression of its ligands (chemoattractants for lymphocytes) - CXCL9, CXCL10 or CXCL11 and endothelin receptor type B was not different according to metastatic status. GITR and FOXP3 expression was significantly higher in cancers vs. normals, normal lung parenchyma (p < 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.
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 beta sequencing (TCR; Adaptive, Seattle WA) and multi-parametric 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 0.053 (IQR 0.017 to 0.189). Median productive clonality at each point was 0.03 (IQR 0.06 to 0.2), 0.03 (IQR 0.06 to 0.2), 0.04 (IQR 0.05 to 0.2) 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 the end of treatment with an increase in proliferation. TCR sequencing revealed increase in productive clonality during radiation for patients with a complete response to treatment.

Background: Paraneoplastic neurologic disease (PND) is an aberrant immune-mediated response against the nervous system triggered by occult cancer. The Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic Department of Surgery and Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic.

Methods: Retrospective review was used to record tumor and treatment factors as well as immune-related neurologic symptoms associated with PND and BC. A descriptive analysis was performed of the symptom data. 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. Over 75% of patients benefit from immunotherapy. These data may provide helpful information to providers treating this population of patients.

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 0.053 (IQR 0.017 to 0.189). Median productive clonality at each point was 0.03 (IQR 0.06 to 0.2), 0.03 (IQR 0.06 to 0.2), 0.04 (IQR 0.05 to 0.2) 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 the end of treatment with an increase in proliferation. TCR sequencing revealed increase in productive clonality during radiation for patients with a complete response to treatment.

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+ CETCs 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: RT leads to 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.

First Author: Lauren Elizabeth Colbert, The University of Texas MD Anderson Cancer Center 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 beta sequencing (TCR; Adaptive, Seattle WA) and multi-parametric 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 0.053 (IQR 0.017 to 0.189). Median productive clonality at each point was 0.03 (IQR 0.06 to 0.2), 0.03 (IQR 0.06 to 0.2), 0.04 (IQR 0.05 to 0.2) 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 the end of treatment with an increase in proliferation. TCR sequencing revealed increase in productive clonality during radiation for patients with a complete response to treatment.
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, NGK2D, CD45RA, CD45RO, CCR7 CCL5 and anti-GRP78 antibody (AF488) were added to one of the tubes. A second tube was incubated with IgG-4AF88 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), NGK2D (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 (1.6 ±0.3). CD8 and NGK2D positivity were 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 included triple negative and Her2 negative subtypes. Conclusions: GRP78 expression was evaluated 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 adeno-carcinoma mouse model. The model was created by in vivo passage of 344SQ murine lung cancer cells (p53 R172H) 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 Oli 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 mouse 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 immunosuppressive cells, including 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 reprogramming 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 gemicitabine (G) in patients with mTNBC. One key question 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). Tumor tissues were then analyzed by immunohistochemistry and flow cytometry for T cell markers. The time of CT was 21-day cycle, and (A/CUCC = 2) (800mg/m2) 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+CD127–) 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 (with 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: Mitsuaki 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. We tested whether genetic polymorphisms in CCL5,CCR5 pathway will predict outcomes in metastatic colorectal cancer (mCRC) patients 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 60 yrs, median follow-up 28.9 mos). In vitro experiments were done; 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 rs1799987 T allele had shorter overall survival (OS) compared to the those with any A allele or the CC 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 rs1800789 G allele and high VEGF-A levels at baseline (PF5) 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: 0.45, 95%CI: 0.24–0.77, P = 0.002); pts carrying any CCR5 rs1799987 T allele had longer PFS and OS (P = 0.025 and P = 0.038, respectively). No significant difference was shown in pts with either A/A or CC 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 A/A variant. Conclusion: 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.

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Algorithmic prediction of response to checkpoint inhibitors: Hyperprogressors versus responders. 

**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:** For 87 patients classified as CR, PR, or SD the PPV >96% for responders and a NPV >90% for non-responders was achieved with the expression 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 resulting 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.

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Baseline cell-free DNA (cfDNA) and metabolic tumor volume (MTV) independently predict outcome in metastatic chemorefractory colorectal cancer (mCRC). First Author: Erwin Wolff, 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 the outcome of patients with mCRC before 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 Cantal and O’Quigley’s method. MTV, cfDNA, age, gender, Body Mass Index (low, normal, high, obese), ECOG PS, number of chemotherapies (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 co-efficient = 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 cm³; 100-300 cm³; > 300 cm³). 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 1 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 1 vs 6; < 0.001) were identified patients with much contrasted outcomes. Conclusions: Baseline cfDNA and MTV along with BMI parameters predict outcome in patients with mCRC before regorafenib. 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.

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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 Oncología, 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-PECT, 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-PECT 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 agnoses 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, cytokosel 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 hypothesis of an IBP in early response.

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Tumor Biology

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 y); 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, amylas en carcinoma, 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 characterizations 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, >1/3 of pts attained SD≥6 months.OPHNF: Further clinic 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 Kaira 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™-quiescent cancer cells (QCCs) are a quiescent, epigenetically plastic, and chemotherapy resistant subpopulation initially identified in experimental cancer models. Here, we asked whether AKT1™ 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 AKT1™ / H3K9me2 low / HES1™ 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 H3K9me2 and HES1 were differentially expressed between 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 inhibiting 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 pretreatment. Fusions involved NTRK1/2/3 were verified by next-generation sequencing (NGS) in 7, forming the study cohort. Fusions involved NTRK1 (6) and NTRK3 (1) with 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 adenocarcinomas, including 2 invasive mucinous adenocarcinomas and 1 adenocarcinoma with neuroendocrine features. Of the 3 remaining non-small cohort cases, 1 was a non-kras-driven MSI-H, and 1 was an NTRK2 intragenic deletion disrupting the exon 18 3’ splice site, and 1 was an NTRK2 alteration detected by FISH but not verified by NGS and with a concurrent HER2L755P 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 oncogetic 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; ≥ 45 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 is p < 0.05. 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 (45%, 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 FGFR3 (28.7%, 10.4%; n = 107; p = 0.034), FGFR2 (26.7%, 9.1%; n = 107; p = 0.019), FGFR1 (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 non-containing, NTRK1/2 alterations (67.4%, 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 GD-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. Apotosis 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 confirmed mRNA NP-mediated systemic restoration of PTEN function in PTEN-null cells and documented 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 suppression (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 pretreatment 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 (2.200 genes) and identified 244 fumarate hydratase (FH) alterations in 49 patients with non-small cell lung cancer. Key cancer genomic 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 Benjamin-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 carcinomas (60-80%). These FN events were observed in 17% of patients where FH mutations were identified in the remaining 237 patients. Conclusion: These findings suggest that tumors with β-catenin pathway alterations are defined by a more metastatic phenotype 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, Foundation 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 (GA) 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, 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 care to evaluate the full spectrum of GA (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 prostate cancer, led to the discovery of a frequency that suggests de-repression of metabolic pathways could contribute to mRNA expression changes and contribute to tumor 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.

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Induction of a BRCA1/2 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-Hydroxymuconate (2HG) exists as two enantiomers, R-2HG and S-2HG, and both are implicated in tumor progression via their inhibitory effects on α-ketoglutarate (αK-G) 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 re-capitated by treatment with either 2HG enantiomer in cells with intact IDH1/2. We performed a comprehensive series of studies that directly implicate two αK-G-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 protein and 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 and cell viability 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.

Antitumor activity of indenoisoquinoline inhibitors of topoisomerase 1 (TOP1) via apoptosis and autophagy/cytotoxic 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 vivo data indicated that all 3 compounds inhibited TOP1 and killed tumor cells. We also reported that gH2AX had been reported that 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 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 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.

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 clinical pathological variables in resected NSCLCs. 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 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 PHLP4, 32(20.9%) with PIK3R1 and 21(14.1%) with TP53. The presence of PIK3 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 LTP widely used in clinical practice. However, positive PD-L1 exp was correlated with PIK3R1 and TP53 mts , warranting further investigation as potential modulators or surrogate of positive PD-L1 expression.

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. Method: To improve neoantigen identification, we extended standard sequencing and informatics methods. We developed an augmented and content enhanced (ACE) exome sequenced at 200X to identify neoantigens from indel and peptide phasing, high accuracy HLA typing, TCR interaction predictors, and standard variation pipelines based on MHC binding algorithms, we developed RNA, we optimized our ACE transcriptome for FFPE tissue. To improve mutation detection, building a robust, validated neoantigen identification platform suitable for clinical applications has been challenging due to the complex processes involved. However, positive PD-L1 exp was correlated with PIK3R1 and TP53 mts , warranting further investigation as potential modulators or surrogates of positive PD-L1 expression.

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**11590**  
Poster Session (Board #230), 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 CBP, and investigating its role in regulating androgen receptor expression and function.

**Methods:** Binding of CCS1477 to p300 and CBP, and BRD4, was measured in a surface plasmon resonance (SPR) assay. Potency and functional activity (p300/CBP and CBP, and CBP, and BRD4) in 22Rv1 and LNCaP xenograft models.

**Results:** CCS1477 binds to p300 and CBP with high affinity (Kd = 1.3/1.7 nM) 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 IC50. Inhibition of p300/CBP also reduces c-Myc, KLK3 and TMPRSS2 gene expression

**Conclusion:** Taken together these data support the clinical testing of CCS1477 in castrate resistant prostate cancer by down-regulation of AR, AR-V7 and c-Myc expression and function.

**11591**  
Poster Session (Board #231), 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 phosphatidylinositol-3-kinase (PIK3) 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 ≥ 2.0 and the criterion of Cappuzzo. The amplification of the PIK3CA was copy numbers ≥ 4.0. We established the patient-derived xenograft (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 confirmed with dual MET/PI3K amplification. The two stage IV 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 (NCT02776027). In the PDX mouse model experiment, we found three single- and triple-kinase inhibitors monotherapy and the combination of the two inhibitors showed a stronger and longer-lasting growth inhibition in PDx models. The addition of taselisib to bozitinib or crizotinib monotherapy provided obvious enhanced activity. Regrettably, two mice died because of the toxicities of the crizotinib+taselisib combination.

**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 #232), 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 is correlated with poor prognosis in patients with ER+ breast cancer. It is essential to understand the impact of DLC1 and its functional network in regulating tumor growth 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 regulating tumor growth and metastases. Low expression of DLC1 is correlated with poor prognosis in patients with ER+ breast cancer. It is essential to understand the impact of DLC1 and its functional network in regulating tumor growth and metastases. Low expression of DLC1 is correlated with poor prognosis in patients with ER+ breast cancer.

**Methods:** Stable knock-in of T47D-DLC1-FL knock-in cells was assessed for 2 weeks using clonogenic assay. Proteomic and phosphopeptide enrichment assays (Peptide ID Tigo62 Mouse Breast Cancer Cell Lines) were used to identify the best candidates 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 basis of altered growth phenotype. The two stage IV patients received the treatment of vehicle control, bozitinib, crizotinib, taselisib (PI3K inhibitor), bozitinib+taselisib, or crizotinib+taselisib, respectively.

**Results:** Taken together, these data support the clinical testing of CCS1477 in castrate resistant prostate cancer by down-regulation of AR, AR-V7 and c-Myc expression and function.

**Conclusion:** Taken together, these data support the clinical testing of CCS1477 in castrate resistant prostate cancer by down-regulation of AR, AR-V7 and c-Myc expression and function.

**11593**  
Poster Session (Board #233), 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 (31.6%), brain (22.7%), and lung (20.7%) (Table). Thirty-six percent of pts (N = 423) had ≥1 alteration. The most frequent alterations (characterized and variants of unknown significance (VUSs)) were in TP53 (32.5% of pts), followed by EGFR (13%) and KRAS (12.5%). Further analysis showed that the addition of taselisib to bozitinib or crizotinib monotherapy provided obvious enhanced activity. The two stage IV patients received the treatment of vehicle control, bozitinib, crizotinib, taselisib (PI3K inhibitor), bozitinib+taselisib, or crizotinib+taselisib, respectively.

**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.

**Characteristics**  
Total patients, N = 670

| Turn over time (median, 95%;c range) | 15 days (15-16, 7-35) |
| Common Tumors | 213 (31.8%) |
| Gastrointestinal | 152 (22.7%) |
| Brain | 139 (20.7%) |
| Lung | 55 (8.2%) |
| Head and neck | 423 (63.1%) |

*pCharacterized alterations and VUSs*
ABC2G and TOP-1 mRNA expression as predictive biomarkers for adjuvant FOLFIRI treatment in stage III colon cancer patients: Results from the PETACC-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 ABC2G and the 75 percentile TOP-1 mRNA expression data were used to allocate the patients into one of two groups: One with high ABC2G 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 ABC2G 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 ABC2G and TOP-1 measurements.

First Author: Nils Brunner

11594 Poster Session (Board #294), Sat, 1:15 PM-4:45 PM

11595 Poster Session (Board #295), Sat, 1:15 PM-4:45 PM

Tumor Biology

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%) 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 patients were treated at an average 112 months (range 16-162 months) post diagnosis. 74% of patients received ALK inhibitors. The TMB by CGP for ALK fusion positive patients was 600X. Tumor mutational burden and TMB were not significantly different between NSCLC and non-NSCLC ALK fusion positive patients. ALK fusion positive patients were heterogeneous in tumor mutational burden. ALK fusion positive NSCLC patients had significantly lower TMB (mean 5.01 mutations/Mb) than non-ALK altered non-NSCLC (p=0.006). Non-NSCLC ALKfusion 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.

First Author: Nils Brunner

11596 Poster Session (Board #296), 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 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 patients were treated at an average 112 months (range 16-162 months) post diagnosis. 74% of patients received ALK inhibitors. The TMB by CGP for ALK fusion positive patients was 600X. Tumor mutational burden and TMB were not significantly different between NSCLC and non-NSCLC ALK fusion positive patients. ALK fusion positive NSCLC patients had significantly lower TMB (mean 5.01 mutations/Mb) than non-ALK altered non-NSCLC (p=0.006). Non-NSCLC ALKfusion 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.

First Author: David James Pinato

11597 Poster Session (Board #297), Sat, 1:15 PM-4:45 PM
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™, n = 10,000) 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 cell lines with co-expression of truncating mutations in RASA1 (LCL103H and H1838), or both (EPCL272H). 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 < 0.02) and KRAS (p = 0.02) mutations. Unexpectedly, RASA1 truncating mutations had a strong tendency to co-occur with NF1 truncating mutations (p < 0.001), 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.

Conclusions: Knockdown of RASA1 in HBECs activated signaling downstream of RAS and promoted cell growth. Conversely, restoration of RASA1 expression in RASA1-KRAS Δ50 mouse models reduced MAPK and PI3K signaling with inactivation of only one of these two RasGAPs showed moderate and variable sensitivity to inhibitors of MEK (trametinib) or PI3K (GDC0941, P1103), EPCL272H cells (with concurrent RASA1/NF1 mutations) showed notably more profound sensitivity (IC50: 0.040 μM 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 potentially actionable driver in NSCLC. Patients whose tumors show this distinctive genetic subtype 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: Sant Schwartz, NantOomics, 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 O6-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 metastatic colorectal cancer (mCRC) receiving TMZ. All mCRC patients whose tumors expressed MGMT were stratified into tertiles based on the limit of quantitation from a concentration curve. The Mantel-Cox log-rank test was used for survival comparisons.

Results: MGMT protein was detected in 13 of 24 (54.2%) colorectal tumor samples (range: 229.3-784.8 amol/ug). The overall survival rate was 29%. Patients with MGMT protein levels below a cutoff of 200 amol/ug (n = 11) had notably higher response rates than patients with MGMT protein levels above a 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 = 0.95, 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.
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 signature. ICOS expression was analyzed by IHC in a subset of indications based on in silico analysis. ICOS expression on intra-tumoral Tegs 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 with 3,800 samples using multiplex immunofluorescence and 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 PD1L expression identified subsets of tumors in multiple indications with high ICOS but low PD1L expression. Conclusions: These data support prioritization of specific tumor types the ICONIC trial.

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 in CA has been tested in 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 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 = 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 METABRIC 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 (p = 0.93, p < 10^-4). In the TCGA dataset, high CA20 score was associated with 3.8- and 5.7-fold worse overall survival (OS) 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 (p = 0.95, p < 10^-4). 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.

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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.

**Background:** PD-1 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). Positive expression was defined as > 5%. 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 yrs. Of case pts with available VL, mean 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%, 92%) of controls. PD-1 expression on TIL was positive in 42% (87%, 56%) 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:** Lung CA HIV+ 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).

**Background:** Validated biomarkers of response to immune checkpoint inhibitors are needed. Methods: INSPIRE (NCT02644369) is a patient-driven study to comprehensively evaluate changes in genomic and immune landscapes in tumors and blood of patients (pts) treated with pembrol (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 (HGSO), 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 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 viable 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 HGSO, 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, 2, 3, 4, 5 were: lymph nodes (42%, 15%, 42%, 67%, 33%); liver (63%, 56%, 15%, 51%, 22%); skin (99%, 52%, 81%, 100%, 31%). **Conclusions:** This report provides robust technical feasibility data to plan immune and molecular characterization of tumor and blood-based biomarkers in pts receiving PCI. Clinical trial information: NCT02644369.

**Tumor 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 | 3.5 (0-6) | 1.65E6 (0.19-3.5E6) | 76, 63, 101, 10, 5 |
Liver | 3.5 (0-6) | 3.2E5 (2.0E5-6.4E5) | 14, 14, 14, 74, 74 |
Skin | 3.5 (0-6) | 1.65E5 (0.19-3.5E5) | 86, 71, 29, 14 |
Other | 3.5 (0-6) | 1.65E5 (0.19-3.5E5) | 55, 56, 16, 8, 8 |

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Variable DNA mismatch repair-associated gene profiles in colorectal versus uterine cancers. First Author: Taban 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 (22.2%) 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%) 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 (8/32 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-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.

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 immunemediated 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 RIPK3 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 RIPK3 or MLKL are associate to loss of TPS3 or FANCAGenes, complex karyotype and advanced age. COKHR model with RIPK1 or MLKL loss, BRACA1 loss, TPS3 mutation, FANCA loss, secondary disease and diagnosis karyotype considered as categorical variable shows that necroptotic deficiency (HR 1.98, 95% CI 0.98 - 3.7, p = 0.066) and TPS3mutation , 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. However, 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 to chemotherapy promoting ICD mechanism. Acknowledgment: ELN,AIL,AIRC, progetto Regione-Universita 2010-12, FP7 NGS-PTL project HARMONY.
Effect of Wnt5a on aggressiveness of ER-positive breast cancer and cancer cell migration through JNK-ALCAM pathway. First Author: Yoshi 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 were 81.1% and 100% in breast cancer.

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 (P < 0.001), high nuclear grade (P = 0.004), and lymphatic invasion (P = 0.001).

Conclusion: Wnt5a expresses in ER-positive breast cancer and could be a novel prognostic factor of ER-positive breast cancer.

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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 200nm tip indenting and measuring stiffness of thousands of locations within 60-180 minutes. 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 biopsy display stiffness profiles distinct from surrounding normal tissue. Breast cancer subtypes were distinguished by their nanomechanical properties only. We 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 demonstrate 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 to optimize specific cancer diagnosis, orientate therapy choice and support patient follow up.

11620 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+) were 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 LN, 14 ER+/HER2-, 3 HER2+) were used. 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 HER2 (p = 0.049), p-HER2 (p = 0.049), p-IGFR (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 = 0.098), 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, HER3 and p-4EBP1 are overexpressed in HER2+ LN mets. Lum A LN mets showed higher levels of p-IGFR, p-Akt, p-4EBP1 vs Lum B LN mets which had higher levels of p-MEK1/2 and p-MEK1/2. These data suggest different signaling pathways in BC mets compared to primary BCs. Analyses of 60 pts' matched primary BC/LN samples will be presented.

11621 Molecular landscape of BRAF mutations in large cell neuroendocrine carcinoma of the 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). Here we present a focused analysis of BRAF mutations in this population. Methods: Comprehensive genomic profiling of tumor tissues was performed from all 66 patients with biopsy proven L-LCNEC. Specimens were either from a primary lung lesion or metastatic site. Results: 14 unique BRAF alterations (mutations, translocations) were identified in 13 patients. The importance of biomarker driven therapy is subsequently highlighted here. These results are compared to the published literature. 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.

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results:

We found several genes preferentially deleted, including TP53, HRAS (4.1%), PTEN (0.9%), FAM123 (3.2%), and CDKN2A (4.2%), while deletions of RB1 (4.6%), CASK (3.5%), and RB1 (4.6%) were also observed. These findings suggest the importance of these genes in the development and progression of cancer. Additionally, we observed a high frequency of gains in CDK4 (3.4%), CDKN2A (4.2%), and TP53 (4.2%), indicating their potential roles in cancer development.

Conclusions: These findings highlight the importance of microarray analysis in identifying novel genetic alterations in cancer. This approach can potentially lead to the discovery of new therapeutic targets and provide insights into the molecular mechanisms underlying cancer development. Further studies are needed to validate these findings and explore their clinical implications.

ACKNOWLEDGMENTS

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REFERENCES


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-FLI1 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 in 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 sequential 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-II 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 completed 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 23th 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 (10 mg daily) alone for 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 received metformin XL plus sirolimus. The pharmacodynamic (PD) biomarkers were collected on days 8 and 22 of each cycle. The primary endpoint was to compare the change in PD biomarker phospho-p70S6K in peripheral blood T cells 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 arm 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.

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