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Abstract Book of the 41st ESMO Congress (ESMO 2016)

7–11 October 2016, Copenhagen, Denmark

Guest Editors:

ESMO 2016 Congress Scientific Committee
# Abstract Book of the 41st ESMO Congress (ESMO 2016) Copenhagen, Denmark, 7–11 October 2016

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basic science

10 Dissecting the roles of Fra proteins in lung adenocarcinoma

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1Genes, Development and Disease, CNIO-Spanish National Cancer Center, Madrid, Spain, 2Molecular Oncology, CNIO- Spanish National Cancer Center, Madrid, Spain

Background: Lung cancer is a life-threatening disease with increased incidence worldwide. Most patients are diagnosed with advanced disease, and as a result, the 5 year survival rate is among the lowest in cancer. Among all lung cancer, 85% are non small lung ADC. K-Ras mutation is the most common in NSCLC, but no drugs that target K-Ras directly or indirectly have yet been discovered. Therefore, there is a need to find a druggable target that can help in the treatment of lung cancer patients. Fra-related antigen 2 (Fra-2), a member of AP-1 transcription factors, has been shown to be activated by K-Ras signaling, as well as deregulated in many cancer types.

Methods: Prognosis value of Fra-2 mRNA expression level was assessed in transcriptomic data from 1928 NSCLC patients through an online survival analysis software. We generated a genetic engineered mouse model (GEMM) for Fra-2 inactivation and p53 inactivation. Fra-2 and p53 inactivation, and mutant K-Ras expression, are induced simultaneously by infection with a Cre-expressing Adenovirus delivered intra-nasally. Development of lung tumours was longitudinally monitored by micro-CT. Dissecting the roles of Fra proteins in lung adenocarcinoma

Results: Fra-2 mRNA high expression was found to be significantly correlated to poor outcome in this ADC patient cohort. Genetic inactivation of Fra-2 in this lung cancer model prolongs the survival of the mice compared with heterozygous Fra-2-2 by decreasing tumor incidence, number and volume.

Conclusions: Our results identify a new potential therapeutic target in K-Ras mutated lung ADC.

Legal entity responsible for the study: A. Alfraidi

Funding: World Wide Cancer Research formerly AICR

Disclosure: All authors have declared no conflicts of interest.

Lenvatinib mesilate (LEN) enhanced antitumor activity of a PD-1 blockade agent by potentiating Th1 immune response

Y. Kato1, X. Bao2, S. Macgrath3, K. Tabata1, Y. Hori1, S. Macgrath2, K. Tabata1, Y. Hori1, S. Tachino1, M. Matijevici2, M. Musteanu2, M. Barbacid2, E. Wagner1

1Eisai Co., Ltd., Fukuoka, Japan, 2Eisai, Inc, Andover, MA, USA

Background: LEN selectively inhibits the kinase activity of VEGFR1-3, FGFR1-4, KIT, PDGFRα, and RET, which are involved in tumor angiogenesis and proliferation in several cancer types. Currently, Phase Ib/II clinical trials of the combination of LEN and pembrolizumab (a monoclonal antibody [mAb] that blocks the interaction between PD-1 and its ligands) are ongoing for selected types of cancer including melanoma and renal cancer. In order to understand the anti-tumor effect and mechanism of action of the combination of LEN and PD-1 blockade treatment, we analyzed immune response in syngenic murine tumor models.

Methods: We examined antitumor activity of combination treatment of LEN (10mg/kg, qd) and anti-pd1 PD-1 mAb (500µg/mouse, twice weekly) against LLC1 murine lung carcinoma, H22 murine hepatocellular carcinoma, and CT26 murine colon cancer in syngenic mouse models. For immune population analyses, tumor or spleen samples were analyzed by flow cytometry. The expression of solute factors and genes was detected by ELISA or qPCR, respectively. We conducted a BioMap human cell co-culture system analysis with peripheral blood mononuclear cells, endothelial cells, and H1299 human lung cancer cells to evaluate effects of each single agent and combination treatments on Th1/Th2 immune response.

Results: Combination of LEN with PD-1 mAb showed more potent inhibitory activity against tumor growth in all 3 models compared with each single agent. Notably, complete tumor regressions were detected in some mice with combination treatment in the H22 syngeneic mouse tumor model. Re-inoculation of fresh H22 cells into these cured mice was rejected. BioMap analysis showed that PD-1 mAb inhibited both Th1 and Th2 cytokines, LEN decreased Th2 cytokines, and combination treatment increased Th1 cytokines but decreased Th2 cytokines. ELISA and qPCR analysis also showed that Th1 cytokines were increased but Th2 cytokines were decreased with combination treatments in the LL/2 and CT26 syngeneic mouse models.

Conclusions: The results indicate that the combination of LEN with PD-1 mAb was more effective than single-agent treatment in multiple syngeneic tumor models and was accompanied with a potent antitumor immune response.

Legal entity responsible for the study: Eisai Inc.

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Metallotionein 1H functions as a tumor suppressor in hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) remains a major cause of cancer-related death worldwide. Metallotioneins (MTs) are low-molecular weight, cysteine-rich proteins, which are overexpressed in many types of cancer. In our previous study, we identified MT1H as an HCC-specific tumor suppressor protein. However, the role of MT1H in the development and progression of HCC remains unknown.

Methods: We performed in vitro and in vivo experiments to investigate the effect of MT1H on HCC cell proliferation and invasion. We also analyzed the expression of MT1H in HCC tissues and compared it with healthy liver tissues.

Results: We found that knockdown of MT1H in HCC cells significantly increased cell proliferation and invasion in vitro. In vivo, we observed that MT1H-deficient HCC cells formed larger tumors and were more invasive compared to WT HCC cells. Furthermore, we observed that MT1H levels were lower in HCC tissues compared to healthy liver tissues.

Conclusions: Our results suggest that MT1H functions as a tumor suppressor in hepatocellular carcinoma. Further studies are needed to understand the mechanism by which MT1H inhibits HCC growth and invasion.

Legal entity responsible for the study: Y. Zheng

Funding: 1st People’s Hospital of Hangzhou, Hangzhou, China

Disclosure: All authors have declared no conflicts of interest.
proteins, and classified into multiple classes. One of the MT species, MT1H, is down regulated in HCC. However, the roles of MT1H in HCC are not fully understood.

**Results:**
Deletion of AMPKα1, but not AMPKα2, exhibited a significant reduction in cellular proliferation of A549 cells and an increase in apoptosis, along with an increase in the expression of the cell cycle inhibitor P21. These results suggest that AMPKα1 is a negative regulator of cell proliferation in these cells.

**Conclusions:**
AMPKα1 knockdown in A549 cells resulted in increased cell proliferation and decreased apoptosis, indicating that AMPKα1 plays a role in regulating cell cycle and apoptosis in these cells.

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2. P. Song, Y. Ding, Q. Lu, M.-H. Zou

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**Conclusion:**
AMPKα1 knockdown in A549 cells resulted in increased cell proliferation and decreased apoptosis, indicating that AMPKα1 plays a role in regulating cell cycle and apoptosis in these cells.
**Results:** Treatment with each EGFR-TKIs in combination with LDE225 resulted in a significant inhibition of cell proliferation and a strong induction of apoptosis as compared to single agent treatment. Additionally, combined treatment significantly decreased the invasive and migratory abilities of resistant cells. The combination of osimertinib and LDE225 appeared to be the most effective in reverting resistance to EGFR-TKIs. Combined treatment caused repression of tumor growth in vivo in nude mice.

**Conclusions:** Our study further support the role of Hedgehog pathway activation as an important mediator of resistance to EGFR targeting drugs, also in the T790M scenario. In addition, it demonstrates that addition of a hedgehog inhibitor to an EGFR-TKI in tumors, which had developed resistance to third generation inhibitors, provides meaningful responses.

**Legal entity responsible for the study:** Second University of Naples

**Funding:** AstraZeneca

**Disclosure:** All authors have declared no conflicts of interest.

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**SYM004, a novel generation anti-EGFR inhibitor, is able to overcome acquired resistance to cetuximab such as MET activation, ERBB2 amplification and EGFR mutations, in colorectal cancer models**

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**Background:** The anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) cetuximab and panitumumab are effective in a subset of RAS/BRAF Wild-Type (WT) metastatic colorectal cancers (mCRCs). Despite RAS-driven selection, not all metastatic tumors respond to EGFR inhibitors and the onset of secondary resistance limits their clinical benefit.

**Methods:** We have tested, in vitro and in vivo, the effects of novel generation anti-EGFR inhibitors such as SYM004 in a panel of colorectal cancer (CRC) models with acquired resistance to cetuximab that we have generated in our laboratory. SYM004 is a 1:1 mixture of two recombinant human mouse chimeric mAbs directed against non-overlapping epitopes of the EGFR. The binding site of the two antibodies is different from cetuximab. A unique feature of SYM004 is its ability to mediate rapid EGFR internalization and subsequent degradation of internalized receptors via EGFR cross-linking.

**Results:** SYM004 shows a potent anti-proliferative effect in cetuximab-resistant CRC cells. In particular we have already demonstrated that in cetuximab-resistant CRC cell lines, cell proliferation, and survival pathways are activated by MET. Interestingly overexpression of TGF-α, a specific EGFR ligand, induced formation of EGFR-MET hetero-dimers, with subsequent MET phosphorylation and activation. SYM004 induces reduction on MET phosphorylation in these cell lines. SYM004 treatment determined also a significant induction of apoptosis in cetuximab-resistant CRC cells and a strong anti-proliferative activity by inhibition of phospho-MAK and phospho-AKT in these cell lines. Moreover, in two other two models of cetuximab-resistant CRC cell with HER2 amplification or EGFR S492R mutation, SYM004 is able to overcome acquired resistance to cetuximab throw inhibition of proliferation and MAPK/AKT pathways activation. The antitumor activity has been confirmed by the in vivo xenografts CRC models.

**Conclusions:** These results suggest that the treatment with SYM004 could be a strategy for overcoming resistance to first generation of anti-EGFR therapies in CRC.

**Legal entity responsible for the study:** Second University of Naples

**Funding:** Sympogen

**Disclosure:** All authors have declared no conflicts of interest.

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**Recombinant AAV gene therapy for the treatment of EGFR positive lung cancer**

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**Background:** Gene therapy using recombinant adenov-associated virus (rAAV) encoding monoclonal antibody (mAb) sequence injected into mice muscle has been shown to produce sustained level of serum antibody level capable of protecting animals from infectious disease in mouse models. We aim to develop a protocol to achieve a therapeutic serum level of 17A7, an anti-epidermal growth factor receptor (EGFR) mAb in mouse models for the treatment of EGFR-positive lung cancer.

**Methods:** rAAV encoding 17A7 light and heavy chains driven by mCK, a muscle specific promoter (AAV8-17A7) was produced. AAV8-17A7 was administered intra-muscularly to mice in all studies. Seral bleeds were performed at appropriate intervals to monitor 17A7 levels. Detection of serum 17A7 was done by ELISA with human EGFR (hEGFR) antigen. In dose escalation studies, different doses of AAV8-17A7 vector were administered to healthy C57/B6 mice. For tumour protection studies, 1x1011 g.v. of AAV8-17A7 were administered followed by tumour inoculation 6 weeks later, either subcutaneously (subcutaneous model) or intravenously (metastatic model). Human A431 luciferase tumour was inoculated in Balb/C nude mice whilst murine 3LL-D122 luciferase tumour was inoculated in C57/B6 mice. Tumours were monitored using caliper measurements and in vitro imaging system (IVIS).

**Results:** ELISA using hEGFR was able to detect serum 17A7 in mice following AAV8-17A7 administration. Higher dose of viral vector results in higher dose of detectable serum 17A7. In Balb/C nude mice with subcutaneous A431 luciferase tumours, smaller tumours with lower luminescence signal were observed in mice administered with AAV8-17A7 compared to mice injected with IM PBS. Bigger tumours with higher luminescence signal were observed in mice given IV 17A7 compared to mice administered with AAV8-17A7.

**Conclusions:** We have developed a protocol to administer AAV8-17A7, a recombinant AAV encoding 17A7, an anti-EGFR antibody that could offer protection against subcutaneous A431 luciferase tumours in Balb/C nude mice compared to PBS control. Similar protection experiments in both subcutaneous and metastatic Lewis lung carcinoma models using murine 3LL-D122 cells as well as in metastatic A431 xenograft model are ongoing and results will be updated.

**Legal entity responsible for the study:** National Institute for Biological Standards and Control

**Funding:** National Institute for Biological Standards and Control

**Disclosure:** All authors have declared no conflicts of interest.

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**Efficacy of sequential treatment with first, second and third generation EGFR inhibitors and role of Hedgehog pathway in the acquisition of resistance in in vivo NSCLC models**

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**Background:** The management of EGFR mutant NSCLC has witnessed the development of first, second and third generation tyrosine kinase inhibitors (TKIs) reaching a substantial improvement in disease outcome. However, data on the optimal sequence of these therapies is needed.

**Methods:** An in vivo model of acquired resistance has been obtained by treating nude mice xenografted with the human EGFR mutant (del e19) NSCLC cell line, HCC827, with a sequence of first, second and third generation EGFR-TKI. Mice were randomized to erlotinib or gefitinib in first line treatment, resistant tumors were re-implanted in mice and randomized to afatinib +/− cetuximab. First and second generation EGFR-TKI resistant tumor was again re-implanted and randomized to osimertinib or standard chemotherapy with cisplatinum-pemetrexed.

**Results:** In the first line treatment, an initial dose-dependent decrease in tumor volume with subsequent development of acquired resistance was evidenced in the majority of tumors with a response rate (RR) of 60%. In the second step, while afatinib treatment resulted in a RR of 85%, mostly represented by partial responses, the combination of afatinib plus cetuximab displayed a RR of 100% (85% complete responses). In the third step, although none of resistant tumors was T790M +, treatment with osimertinib resulted in a RR of 71% (including one complete response lasted more than 10 weeks).

**Chemotherapy caused predominantly stable diseases lasted less than 5 weeks. Protein and gene expression analysis on protein extracts from tumors with acquired resistance showed a progressive increment in SMO and Gli1.

**Conclusions:** Osimertinib is effective after failure of first and second generation EGFR-TKIs independently from the T790M presence. These experiments confirm the role of Hedgehog pathway as an important mediator of resistance to EGFR inhibition.

**Legal entity responsible for the study:** Second University of Naples

**Funding:** AstraZeneca

**Disclosure:** All authors have declared no conflicts of interest.
Legal entity responsible for the study: Second University of Naples

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Disclosure: All authors have declared no conflicts of interest.

Reversion of mesenchymal behaviour by AZD9291 (osimertinib) in EGFR mutant NSCLC cell lines resistant to first generation EGFR tyrosine kinase inhibitors

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Background: Resistance to first-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs) is mainly mediated by the acquisition of the EGFR secondary mutation T790M and/or by the acquisition of a mesenchymal phenotype. We explored the occurrence of epithelial to mesenchymal transition (EMT) characteristics in EGFR-TKIs resistant NSCLC models, with and without acquisition of T790M mutation, and the ability of novel generation EGFR inhibitors to revert the resistant phenotype.

Methods: The following human NSCLC cell lines harboring EGFR activating mutations were used: HCC827 and PC9 NSCLC cell lines harboring EGFR activating mutation (del 746-750), the PC9-T790M (T790M+) and the HCC827-R (T790M-) gefitinib resistant cells, and the H1975 carrying both EGFR activating and T790M mutations. The mesenchymal behavior and the effects of a latrunculin and omepratam on resistant cell lines were studied both in vitro, by Western blot analysis, invasion, migration and anchorage-independent growth assays and in vivo, by metastatic assay in mice after tail vein injection with resistant cells.

Results: All gefitinib resistant cell lines, H1975, HCC827GR and PC9, T790M, exhibited higher expression of the mesenchymal proteins, such as vimentin, Slug and VE-Cadherin and lost of E-Cadherin, as compared to gefitinib sensitive cells, with increased ability to migrate, invade and grow in anchorage-independent manner. Treatment with gefitinib, and, to a greater extent, with omepratam, strongly inhibited proliferation, migration and anchorage independent colonization forming ability of H1975 and PC9-T790M cells, while effects were similar on HCC827-GR cells in vitro. Metastatic assay in vivo confirmed the superior efficacy of omepratam in T790M+ models.

Conclusions: Collectively, these results suggest that EGFR mutant NSCLC cells resistant to first generation EGFR-TKI develop a mesenchymal phenotype, independently from the acquisition of T790M mutation. In this scenario, omepratam is the most potent agent to overcome resistance and to revert the metastatic behavior of resistant cells.

Legal entity responsible for the study: Second University of Naples

Funding: AntaZeneva

Disclosure: All authors have declared no conflicts of interest.

Efficacy of second and third generation EGFR tyrosine kinase inhibitors, alone or in combination, in T790M-mediated resistance

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Background: The best first-line approach to be used in T790M+ NSCLCs has to be defined. Our aim is to test in T790M+ preclinical models the efficacy of second and third generation EGFR-TKIs, as single agents or in combination with cetuximab or selumetinib. Other four arms of treatments with combination of afatinib/osimertinib have been included.

Methods: We generated CRC cell lines (HCT15 and HCT116) resistant to either a PI3K pathway have a role in primary resistance to anti HER2 drugs, was able to increase apoptosis and decrease the S phase of cell cycle. Inhibition of molecular targets was confirmed by Western Blot (WB) analysis and quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR) the expression and activation status of a panel of

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Disclosure: All authors have declared no conflicts of interest.

HER2 activation and epithelial-mesenchymal transition (EMT) are involved in the acquired resistance to cetuximab in combination with either regorafenib or refametinib

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Background: Many patients do not benefit of this treatment due to some undisclosed mechanisms of primary resistance. Thus, we try to identify the role of PI3K and MAPK pathways activation in a panel of HER2 positive gastric cancer cell lines.

Methods: To evaluate primary resistance to anti HER2 treatment, we selected 3 HER2+ GCCL (SN216, NCLI-N87 and OE 19), and 2 negative (AGS and SNU 484). A somatic mutational analysis was conducted, (Oncomap panel 1.0 by MassArray Sequenom) to better characterize our panel. Microsatellite instability (MSI) by PCR was also investigated. To assess sensitivity, cells were treated with different anti HER2 drugs, trastuzumab and lapatinib. MT2 assays were performed to identify IC50. A PI3K dual mTOR inhibitor (GSK 458) and a MEK inhibitor (Pimasertib) were also tested to explore the role of PI3K and MAPK pathways in primary resistance. Protein expression by western blot (WB) at baseline and after treatment was done. FACS technology was performed to study changes in Apoptosis and Cell Cycle.

Results: Baseline WB, confirmed the overexpression of HER2 in SN216, NCLI-N87 and OE19 cell lines, while AGS and SNU 484 resulted negative. Our cell lines have different mutational profiles. MSI was not detected. In MTT assays, our HER2+ GCCL were sensitive to anti HER2 drugs. At baseline, according to our WB evaluation, both PI3K and MAPK pathways were activated in all cell lines studied. GSK 458 and Pimasertib were tested as single agents and in combination. An anti-proliferative effect of GSK 458 when combined with trastuzumab and lapatinib was detected. Apoptosis and Cell Cycle assays confirmed that inhibition of PI3K pathway, with GSK 458, added to anti HER2 drugs, was able to increase apoptosis and decrease the S phase cell cycle. Inhibition of molecular targets was confirmed by post treatment WB.

Conclusions: Our experiments indicate that PI3K pathway have a role in primary resistance to anti HER2 agents in GCCL.

Legal entity responsible for the study: Valentina Gambardella

Funding: INCLIV A Foundation

Disclosure: All authors have declared no conflicts of interest.

Inhibition of PI3K pathway improves anti HER2 treatment efficacy in a panel of HER2 positive gastric cancer cell lines

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Background: Gastric cancer (GC) represents a major health problem. HER2, when amplified, is the only validated druggable target. Adding trastuzumab, an anti HER2 monoclonal antibody, to first line chemotherapy improves overall survival. However, many patients do not benefit of this treatment due to some undisclosed mechanisms of primary resistance. Thus, we try to identify the role of PI3K and MAPK pathways activation in a panel of HER2 positive gastric cancer cell lines (GCCL).

Methods: To evaluate primary resistance to anti HER2 treatment, we selected 3 HER2+ GCCL (SN216, NCLI-N87 and OE 19), and 2 negative (AGS and SNU 484). A somatic mutational analysis was conducted, (Oncomap panel 1.0 by MassArray Sequenom) to better characterize our panel. Microsatellite instability (MSI) by PCR was also investigated. To assess sensitivity, cells were treated with different anti HER2 drugs, trastuzumab and lapatinib. MT2 assays were performed to identify IC50. A PI3K dual mTOR inhibitor (GSK 458) and a MEK inhibitor (Pimasertib) were also tested to explore the role of PI3K and MAPK pathways in primary resistance. Protein expression by western blot (WB) at baseline and after treatment was done. FACS technology was performed to study changes in Apoptosis and Cell Cycle.

Results: Baseline WB, confirmed the overexpression of HER2 in SN216, NCLI-N87 and OE19 cell lines, while AGS and SNU 484 resulted negative. Our cell lines have different mutational profiles. MSI was not detected. In MTT assays, our HER2+ GCCL were sensitive to anti HER2 drugs. At baseline, according to our WB evaluation, both PI3K and MAPK pathways were activated in all cell lines studied. GSK 458 and Pimasertib were tested as single agents and in combination. An anti-proliferative effect of GSK 458 when combined with trastuzumab and lapatinib was detected. Apoptosis and Cell Cycle assays confirmed that inhibition of PI3K pathway, with GSK 458, added to anti HER2 drugs, was able to increase apoptosis and decrease the S phase cell cycle. Inhibition of molecular targets was confirmed by post treatment WB.

Conclusions: Our experiments indicate that PI3K pathway have a role in primary resistance to anti HER2 agents in GCCL.

Legal entity responsible for the study: Valentina Gambardella

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membrane receptors including HER2, EGFR, AXL, EphA2, VEGFRs, intracellular transducers of MAPK and AKT pathways and Epithelial-Mesenchymal Transition (EMT) markers such as Vimentin, E-cadherin, Snail, Slug.

Results: We found different activation patterns for some of the transmembrane receptors and intracellular transducers among HCT116 and HCT116 resistant clones. In particular, HER2 protein was overexpressed and activated in both Cetuximab-Regorafenib resistant (CR-res) and Cetuximab-Regorafenib resistant (CM-res) cell populations compared to the parental cell line. Moreover, there was evidence of Epithelial-Mesenchymal Transition in the CR-res cell population, suggesting the role of this process in acquired resistance to regorafenib. Experiments to test anti-HER2 drugs in resistant cell lines, as well as Next Generation Sequencing (NGS) approaches in order to detect neo-gene rearrangements, are currently ongoing and will be presented.

Conclusions: Our in vitro preliminary data demonstrated, at least in part, that HER2 protein activation and EMT might play a role in the development of acquired resistance to cetuximab in combination with either regorafenib or regorafenib, suggesting a possible role of anti-HER2 therapies in this setting.

Legal entity responsible for the study: Fortunato Cardiello

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Disclosure: All authors have declared no conflicts of interest.

PD-L1 pathway activation as an escape mechanism of resistance to MEK inhibitor treatment in a human colorectal cancer model

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Background: In patients with metastatic colorectal cancer (mCRC) who receive anti-epidermal growth factor receptor (EGFR) therapies, gene alterations that emerge at relapse converge to activate the RAS-MEK-RAF pathway. MEK is a key downstream effector of the EGFR pathway that should be inhibited to prevent or delay the onset of acquired resistance to anti-EGFR treatment.

Methods: In order to understand the mechanism underlying MEK resistance, SW48 quadruple RAS/RAF/BRAF Wild-Type (WT) colorectal cancer (CRC) cell lines were injected subcutaneously into nude female mice and treated with MEK inhibitor (MEKi). When tumors were resuming growth despite MEKi treatment, mice were sacrificed and tumors were removed, cut in several pieces and used to generate in vitro MEK-resistant cell lines (SW48-MR). To investigate the potential molecular pathways involved in MEK-inhibition, miRNAs from SW48 and SW48-MR cells were extracted and assessed for global gene expression changes by microarray analysis.

Results: Among the genes that were upregulated in SW48-MR versus SW48 we have identified several genes involved in the PD-L1 pathway. In particular the PD-L1 gene was up regulated approximately 10 fold in the resistant cells as compared to parental cells. Moreover, genes overexpressed in MEK-resistant tumor were functionally related in pathways involving immune cell activation, inflammation, and antigen processing and presentation. These results demonstrate an enhanced immune-reactive microenvironment in MEK-resistant tumors.

Conclusions: These results suggest a strategy to potentially improve the efficacy of MEK inhibition by co-treatment with other agents and provide an additional mechanism of therapeutic resistance via modulation of host immune responses.

Legal entity responsible for the study: Second University of Naples

Funding: AIRC

Disclosure: All authors have declared no conflicts of interest.

miRNA-145 promotes differentiation in human urothelial carcinoma through down-regulation of syndecan-1

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Background: A new molecular marker for carcinoma in the urinary bladder is needed as a diagnostic tool or therapeutic target. Candidate markers include miRNAs (miRNAs), which are short, low-molecular-weight RNAs 19-24 nt in length, that regulate genes associated with cell proliferation, differentiation, and development in various cancers. In this study, we investigated the molecular mechanisms by which miRNA-145 promotes the survival of urothelial carcinoma cells and their differentiation into multiple lineages.

Methods: Cell proliferation in the human urothelial carcinoma cell lines T24 and KU7 was assessed by MTS assay. Cellular senescence and apoptosis were measured by senescence-associated β-galactosidase (SA-β-gal) and a TUNEL assay, respectively. Quantitative RT-PCR was used to measure the mRNA expression levels of various genes, including syndecan-1, stem cell factors, and markers of squamous, glandular, or neuroendocrine differentiation. The expression of miRNA-145 in urothelial carcinoma tissues was assessed using RT-PCR. We also examined the effects of syndecan-1 on cell proliferation in vitro by using Sytox Green staining.

Results: Overexpression of miRNA-145 induced cell senescence, and thus significantly inhibited cell proliferation in T24 and KU7 cells. Syndecan-1, a heparin sulfate proteoglycan, expression decreased, whereas the levels of stem cell markers such as
Background: Zoledronic acid (ZOL), a third generation bisphosphonate able to significantly inhibit bone resorption, is currently used for the treatment of breast cancer patients with osteolytic bone metastases. Our previous work showed an effective anticanic role of low-dose ZOL in the inhibition of several processes, such as cell adhesion, invasion, cytoskeleton remodelling and proliferation, in MCF-7 breast cancer cell line. The main aim of our study was to investigate the molecular mechanisms and signaling pathways by which ZOL exerts its anti-tumor effects in breast cancer cells focusing our attention on miRNA expression profile.

Methods: Using a TaqMan Low Density Array Human miRNA microarray analysis, the expression profile of 377 miRNAs was analyzed in MCF7 cells treated for 24h with 10μM ZOL with respect to untreated cells. In addition, the expression of miRNAs specifically induced by ZOL was analyzed in MCF-7, MDA-MB-231 and SKBR3 cells using real-time PCR assays.

Results: A subset of miRNAs was shown to be differentially expressed following the low-dose ZOL treatment, and several cancer-related pathways, including PI3/Akt, MAPK, Wnt, Jak-STAT, TGF-β and mTOR signaling, were predicted as potential targets of these deregulated miRNAs using the DIANA tool miPath software. In particular, a set of 54 miRNAs resulted significantly altered after ZOL exposure, with a group of them being up- or down-regulated, and others induced or silenced by treatment. Most of these miRNAs are unexamined in breast cancer cells. These data are perfectly in agreement with the recent results reported in literature regarding some miRNAs involved in proliferation, bone metastasis development, invasion and therapy resistance in breast cancer.

Conclusions: This work establishes, for the first time, a link between anticancer effects of ZOL and miRNA expression changes, suggesting the involvement of some miRNAs in molecular pathways mediating ZOL activity in breast cancer.

Legal entity responsible for the study: University of Palermo

Disclosure: All authors have declared no conflicts of interest.

miRNA-331-3p inhibits cell proliferation and E7 expression by targeting NRP2 in cervical cancer

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Background: Aberrant expression of microRNAs (miRNAs) is involved in the development and progression of various types of cancers. In this study, we investigated the role of miR-331-3p in cell proliferation and keratinocyte differentiation in uterine cervical cancer cells. Moreover, we evaluated whether neuropilin 2 (NRP2) which are putative target molecules of miR-331-3p regulated the human papillomavirus (HPV) -related oncogene E6 and E7.

Methods: Cell proliferation in the human cervical cancer cell lines SK-GI-H1 and HeLa was assessed using the MTS assay. A functional assay for cell cycle growth was performed using cell viability and cell cycle analysis. Cellular apoptosis was measured using a TUNEL assay. Quantitative RT-PCR was used to measure the mRNA expression of the E6, E7, NRP2, p63, and involucrin (IVL) genes and anti-apoptosis markers bcl2, bclXL, and BAX.

Results: Overexpression of miR-331-3p inhibited cell proliferation, and induced G2/M phase arrest and apoptosis in SK-GI-H1 cells. The luciferase reporter assay of the NRP2 3′-untranslated region revealed direct regulation of NRP2 by miR-331-3p. Gene expression analyses using quantitative RT-PCR in both SK-GI-H1 and HeLa cells overexpressing miR-331-3p or suppressing NRP2 revealed down-regulation of E6, E7, and p63 mRNA and up-regulation of IVL mRNA. We showed that miR-331-3p and NRP2 were key effectors in cell proliferation by regulating the cell cycle and expression of E6 and E7, and keratinocyte differentiation by down-regulating p63 and up-regulating IVL.

Conclusions: Our findings suggest that miR-331-3p has an important role in regulating cervical cancer cell proliferation, and overexpression of miR-331-3p through suppression of NRP2 may contribute to keratinocyte differentiation and may have anti-cancer effects. Our future studies will examine whether miR-331-3p and its target, NRP2, are useful clinical diagnostic and/or prognostic markers for histological and cytological examination using tissue specimens and liquid-based cytology in the screening and diagnosis of cervical cancer.

Legal entity responsible for the study: Nara Medical University School of Medicine, Nara, Japan

Disclosure: All authors have declared no conflicts of interest.

Radioresistance genes in head and neck cancer

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Background: Radiotherapy (RT) is integral in the treatment of head and neck cancer (HNC). Tumors have varying response to RT. Quantifying gene expression and correlating it with outcome can identify genes that influence a tumor’s response to radiation. Our goal is to identify the genes predictive of locoregional recurrence (LRR) in HNC patients treated with RT.

Methods: Patient data was abstracted from a prospectively maintained institutional Total Cancer Care (TCC) database and chart review. All microarray chips were normalized using iterative rank-order normalization method. A supervised Gene Set Enrichment Analysis (GSEA) was performed to determine whether a priori defined gene pathways show statistically significant, concordant differences between groups of samples obtained before and after radiation therapy. 30 well-annotated hallmark gene sets were obtained from Molecular signatures database v.5.1 for GSEA analysis. Linear Models for Microarray Data (LIMMA) was used to identify individual genes with differential expression between the two groups. To explore survival-associated genes, Cox proportional hazard regression analysis was performed with time to local-regional recurrence data of patients who underwent radiotherapy. Further, Spearman’s rank correlation was calculated between expression and survival fraction after 2Gy RT (SF2) of cancer cell lines in NCI-60 panel. Two-sided false discovery rate (FDR) adjusted p-value less than 0.05 is considered statistically significant.

Results: A total of 108 patients were analyzed, of which 49 (45%) were sampled prior and 59 (55%) after receiving RT. There were a total of 48 (44%) LRRs. Thirty eight genes were identified in common with a differential expression in NCI-60, prior receipt
Ado trastuzumab emtansine (TDM1) is a novel antibody-drug conjugate consisting of trastuzumab (TRAS) covalently linked to the highly potent microtubule inhibitory agent DM1 via a stable thioether linker. TDM1 is used in metastatic ErbB2 positive breast cancer patients, previously treated with TRAS and taxane. Although the potential cardiotoxic effects of T-DM1 have not yet been fully elucidated, they can include all the mechanisms of TRAS-related cardiotoxicity, such as blockade of ErbB2/PI3K-Akt and MAPK pathways. Furthermore, since TDM1 is also used in combination with other anti-ErbB2 agents, the risk of cardiotoxic side effects could be further increased. Here, we aim to assess the cardiotoxic side effects of TDM1 in vitro and in vivo.

Methods: To evaluate the cardiotoxic effects of TDM1 in vitro, human fetal cardiomyocytes (HFC) and cardiomyoblasts (H9C2) were treated, for 3 days, in the absence or in the presence of increasing concentrations of TDM1 and TRAS.

Results: TDM1 clearly causes more marked changes in HFC cell morphology, cells, that indeed have not yet been fully elucidated, they can include all the mechanisms of TRAS-related cardiotoxicity, such as blockade of ErbB2/PI3K-Akt and MAPK pathways. Furthermore, since TDM1 is also used in combination with other anti-ErbB2 agents, the risk of cardiotoxic side effects could be further increased. Here, we aim to assess the cardiotoxic side effects of TDM1 in vitro and in vivo.

All authors have declared no conflicts of interest.

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Disclosure: All authors have declared no conflicts of interest.

Role of the Hedgehog pathway in preventing occurrence of resistance to first, second, third generation EGFR-TKIs in first line therapy of NSCLC models with EGFR activating mutations


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Background: NSCLC patients with EGFR activating mutations can be treated with different lines of EGFR tyrosine kinase inhibitors (EGFR-TKIs), and it is still unknown which is the best EGFR-TKIs in first line. This work investigates the best choice of treatment in the first line setting in EGFR mutant NSCLC models.

Methods: The in vivo model of sensitivity is represented by nude mice xenografted with human cancer NSCLC cell lines harboring the EGFR activating mutation (delex19) HCC827, which is known to not develop T790M. Mice have been randomized to receive first line therapy with a first generation EGFR-TKIs (gefitinib), second generation EGFR-TKIs (osimertinib), third generation EGFR-TKIs (afatinib) or control (vehicle). Additionally treatments were continued or not in order to obtain new in vivo models of resistance to each generation of TKIs. Each resistant tumor has been collected and analyzed for gene and protein expression.

Results: According to RECIST criteria, a dose-dependent decrease in tumor volume of almost all mice treated with each inhibitor was evident after 14 weeks of treatment. Response rates were similar among inhibitors. Western blot analysis on protein extract from tumors resistant to afatinib and to osimertinib showed increased levels of Hedgehog related proteins as compared to untreated controls. Preliminary results from gene analysis revealed appearance of SMO mutation (V404M) in one tumor resistant to osimertinib, with an allele frequency of 50%, comparing to baseline. These data demonstrate that, in cell models not developing T790M-mediated resistance, first, second and third generation EGFR-TKIs are equivalent in terms of tumor response. In such models, Hedgehog pathway activation plays an important role as mediator of first line EGFR-TKIs treatment suggesting new strategy of combination of Hedgehog inhibitors with EGFR-TKIs in first line to prevent the occurrence of resistance.

Legal entity responsible for the study: AstraZeneca

Disclosure: All authors have declared no conflicts of interest.

Hypoxia inducible factor prolyl hydroxylase 2 (PHD2) is a direct regulator of epidermal growth factor receptor (EGFR) signaling in breast cancer

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Background: Clinical studies indicate that the family of epidermal growth factor receptors (EGFR/ERBB) has important roles in the progression of breast cancer. Accordingly, many EGFR/ERBB inhibitors are used as drugs for the treatment of this disease. However, hypoxia in solid tumors is believed to contribute to resistance to EGFR/ERBB targeted therapies. A positive correlation exists between the activation of ERBB and the synthesis of hypoxia-inducible factor-1 alpha (HIF-1 alpha), a key regulator of the hypoxic response. Our preliminary results indicate, that the main player of hypoxia-signaling driven HIF-1 alpha degradation prolyl hydroxylase 2 (PHD2) greatly contributes to the stability and signaling of ERBB.

Methods: To characterize the relationships between PHD2 and EGFR in vivo we have analyzed the biospies from breast cancer patients. To further understand the connection between these proteins on a molecular level, we have characterized MDA-MB-231 breast cancer cell line with a stable knockdown of PHD2. EGFR levels of RT, and cox regression analysis of LRR. Upregulation of 26 genes were associated with LRR, the majority of which (22/26, 85%) were significantly elevated in the samples that were previously radiated. Deregulation of 12 genes were associated with LRR, of which 8 (67%) were significantly lower in samples that were previously radiated.

Conclusions: We identify a number of genes with alteration in expression, which may be associated with resistance to radiotheray in HNC. Further validation is necessary in other patient cohorts as well as in vitro studies.

Legal entity responsible for the study: Jimmy J. Caudell

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Disclosure: All authors have declared no conflicts of interest.

26P

Ranolazine partially blunts ado trastuzumab emtansine related cardiotoxicity

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Background: Ado trastuzumab emtansine (TDM1) is a novel antibody-drug conjugate consisting of trastuzumab (TRAS) covalently linked to the highly potent microtubule inhibitory agent DM1 via a stable thioether linker. TDM1 is used in metastatic ErbB2 positive breast cancer patients, previously treated with TRAS and taxane. Although the potential cardiotoxic effects of T-DM1 have not yet been fully elucidated, they can include all the mechanisms of TRAS-related cardiotoxicity, such as blockade of ErbB2/PI3K-Akt and MAPK pathways. Furthermore, since TDM1 is also used in combination with other anti-ErbB2 agents, the risk of cardiotoxic side effects could be further increased. Here, we show the alteration of RS persists even after treatment with RAN (35.7 ± 8.2 %, p > 0.05).

Conclusions: Here we show that in vivo RAN post-treatment reduces cardiotoxic effects due to TDM1, as demonstrated by the recovery of FS, EF and LS values. As expected, RAN increases cell viability of HFC treated with TDM1.

Legal entity responsible for the study: N/A

Funding: Fondi di Ricerca Corrente destinati all’ Istituto Nazionale Tumori Pascale - Napoli

Disclosure: All authors have declared no conflicts of interest.
Funding: AstraZeneca

Legal entity responsible for the study: Activation of mTOR is one of mechanisms of acquiring resistance activated, an alternative signaling pathway was sought and the phosphorylated level of with AZD 4547 by Western blotting and MTT assay. Because PI3K and Akt were not confirmed. The SNU15R and parent SNU16 cell lines were incubated with everolimus human phosphor-RTK kit (R&D Systems).

Background: The fibroblast growth factor - fibroblast growth factor receptor (FGF-FGFR) signaling pathway plays a role in cell proliferation, migration, survival, and angiogenesis. Because approximately 10% of gastric cancers show amplification of FGFR2, inhibition of FGFR2 activation has been regarded as one of therapeutic targets. AZD4547, a selective inhibitor of the FGFR1-3 tyrosine kinases, was developed to inhibit FGFR signaling, however, its efficacy is limited by emergency of the acquired resistance. We tried to clarify a resistance mechanism against the FGFR inhibitor.

Methods: The cell line resistant against the AZD4547 was established using SNU-16 (SNU16R), a FGFR2 amplified gastric cancer cell line, by culturing with increasing concentration of the AZD4547. The expression level of FGFR or phosphorylated FGFR (pFGFR) and downstream signaling molecules was determined by Western blot. Cell viability was measured with MTT assay. Relative level of tyrosine phosphorylation of (pFGFR) and downstream signaling molecules was determined by Western blot. Cell viability was measured with MTT assay. Relative level of tyrosine phosphorylation of (pFGFR) and downstream signaling molecules was determined by Western blot. Cell viability was measured with MTT assay. Relative level of tyrosine phosphorylation of (pFGFR) and downstream signaling molecules was determined by Western blot. Cell viability was measured with MTT assay. Relative level of tyrosine phosphorylation of (pFGFR) and downstream signaling molecules was determined by Western blot. Cell viability was measured with MTT assay. Relative level of tyrosine phosphorylation of (pFGFR) and downstream signaling molecules was determined by Western blot.

Results: Loss of expression of FGFR2 and pFGFR2 was confirmed in the SNU16R cell line by Western blotting. The viability of SNU16R cell line was shown to be increased than that of the parent cell line after incubation with AZD 4547. Change of the FGFR2 downstream signaling pathways was addressed, and upregulated expression level of phosphorylated mammalian target of rapamycin (mTOR) was found. Overexpression of downstream targets of mTOR, such as phosphorylated 4E-BP1 and S6K was also confirmed. The SNU15R and parent SNU16 cell lines were incubated with everolimus or AZD 4547, and inhibition of activated mTOR was observed with everolimus but not with AZD 4547 by Western blotting and MTT assay. Because PI3K and Akt were not activated, an alternative signaling pathway was sought and the phosphorylated level of EphB3 was found to be decreased.

Conclusions: Activation of mTOR is one of mechanisms of acquiring resistance against AZD 4547 in FGFR2 amplified gastric cancer cells. Targeting mTOR could overcome the resistance by inhibition of activation of mTOR.

Legal entity responsible for the study: Korea University Guro Hospital

Funding: AstraZeneca

Disclosure: S.Y. Lee, Y. Jeong, Y. Na, J. L. Kim, D.H. Lee, S.C. Oh: This research was funded by AstraZeneca. All experiments were performed independently from AstraZeneca.

Anticancer activity of the mTOR inhibitor (everolimus) and dual mTORC1/mTORC2 inhibitor (AZD2014) on mouse lymphocytic leukemia both in vitro and in vivo

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Background: The mammalian target of rapamycin (mTOR) controls cell growth and enlargement and has been found to be abnormally wide in a variety of malignancies. Allosteric mTOR inhibitors, which inhibit mTORC1 but not mTORC2, result in feedback activation of Akt signaling, which can attenuate their antitumor activity. AZD2014 is a a second generation mTOR inhibitor that blocks activation of both mTORC1 and mTORC2, and activates apoptosis in cancer cells without activation of Akt signaling. Here, we investigated the therapeutic efficacy of everolimus and AZD2014 in lymphocytic leukemia cell line (L1210) and mouse xenograft model.

Methods: Cytotoxicity effect of AZD2014 and everolimus in L1210 cells was assessed after 24 and 48 h by using cell viability assays, clonogenic survival assays, and cell cycle analyses. Cell cycle, mTOR signal transduction pathway and the relative regulatory molecules were examined in mTOR inhibitor-treated L1210 cells by western blotting to detect protein expression. Then, in vivo anti-leukemic effect of AZD2014 was assessed in L1210 cell-transplanted DBA/2 mice.

Results: AZD2014 significantly inhibited L1210 cell proliferation with an IC50 of 10nM. In contrast, everolimus was a poor growth inhibitor of L1210 cells (IC50 > 200nM). Treatment with AZD2014 was more effective than RAD001 to down-regulate the levels of mTORC1 downstream effectors, including S6K1, 4EBP1, elf4e and a significant decrease in protein levels of rictor, a component of mTORC2 protein. We also observed inhibition of mTORincreased G1 arrest by reducing cyclin D1 and CDK4 levels, which augmented growth inhibitory effect of L1210 cells. In vivo, AZD2014 oral administration significantly inhibited the growth of L1210 cell xenograft in DBA/2 mice, and the mice survival was dramatically improved.

Conclusions: These data indicate that AZD2014 may be a better therapeutic agent than mTORC1 inhibitors to enhance the antitumor activity of lymphocytic leukemia both in vitro and under xenograft model in vivo conditions. Antitumor activity of AZD2014 was inhibited of both mTORC1 and mTORC2 activity and cell cycle arrest, leading to lymphocytic leukemia growth inhibition.

Legal entity responsible for the study: N/A

Funding: Without funding from a Pharma, biotech, or other commercial company.

Disclosure: All authors have declared no conflicts of interest.
Background: In metastatic colorectal cancer (mCRC) the presence of intrinsic and the differentiation of the therapeutic resistance to target therapy is one of the most critical problems in the treatment of patients. The RAS/Raf/MEK/MAPK signalling pathway plays central roles in the intracellular transduction of proliferative signals from activated cell membrane growth factor receptors to the nucleus in cancer cells. MEK activation is an important convergence point involved in the development of drug resistance in mCRC setting. AXL, a tyrosine kinase receptor, plays important roles for cancer progression, invasion, metastasis and drug resistance. We did this preclinical study to evaluate a possible mechanism of MEK acquired resistance.

Methods: CRC (HCT116 and LOVO) cell lines were used. We generated in vitro HCT116 and LOVO cell lines resistant to the MEK inhibitor refametinib. Expression and activation of intracellular pathway were analysed by Western Blot (WB). The effect of foretinib, BAY428 and S49076 (AXL inhibitors) were evaluated by WB assay. Cell cycle and apoptosis were analysed by flow cytometry. Chambers of transwell were used and activation of intracellular pathway were analysed by Western Blot (WB).

Results: We generated, HCT116 and LOVO clones (MEK-R) resistant to refametinib after continuous one-year drug exposure. MEK-R CRC cells have an IC50 value 50 and 100 times higher than parental cells, respectively. We found in the resistant clones a strong activation of pAXL and its downstream pathway (in particular pAKT). Treatment of resistant clones with the different concentrations of AXL inhibitors was able to reduce cell viability accompanied by a marked deregulation of activation of AXL, AKT and MAPK. Further experiments on cell cycle, apoptosis and migration are able to reduce cell viability accompanied by a marked deregulation of activation of pAXL and its downstream pathway (in particular pAKT).

Conclusions: Further investigations are needed to evaluate the combination of anti-proliferative and pro-apoptotic effect of refametinib and axitinib in CRC cell lines.

Legal entity responsible for the study: Department of Clinical and Experimental Medicine ‘F. Magrassi’, Second University of Naples

Funding: Department of Clinical and Experimental Medicine ‘F. Magrassi’, Second University of Naples

Disclosure: All authors have declared no conflicts of interest.

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AXL activation can promote resistance to MEK inhibition in a model of colorectal cancer (CRC)

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Background: In metastatic colorectal cancer (mCRC) the presence of intrinsic and the differentiation of the therapeutic resistance to target therapy is one of the most critical problems in the treatment of patients. The RAS/Raf/MEK/MAPK signalling pathway plays central roles in the intracellular transduction of proliferative signals from activated cell membrane growth factor receptors to the nucleus in cancer cells. MEK activation is an important convergence point involved in the development of drug resistance in mCRC setting. AXL, a tyrosine kinase receptor, plays important roles for cancer progression, invasion, metastasis and drug resistance. We did this preclinical study to evaluate a possible mechanism of MEK acquired resistance.

Methods: CRC (HCT116 and LOVO) cell lines were used. We generated in vitro HCT116 and LOVO cell lines resistant to the MEK inhibitor refametinib. Expression and activation of intracellular pathway were analysed by Western Blot (WB). The effect of foretinib, BAY428 and S49076 (AXL inhibitors) were evaluated by WB assay. Cell cycle and apoptosis were analysed by flow cytometry. Chambers of transwell were used and activation of intracellular pathway were analysed by Western Blot (WB).

Results: We generated, HCT116 and LOVO clones (MEK-R) resistant to refametinib after continuous one-year drug exposure. MEK-R CRC cells have an IC50 value 50 and 100 times higher than parental cells, respectively. We found in the resistant clones a strong activation of pAXL and its downstream pathway (in particular pAKT). Treatment of resistant clones with the different concentrations of AXL inhibitors was able to reduce cell viability accompanied by a marked deregulation of activation of AXL, AKT and MAPK. Further experiments on cell cycle, apoptosis and migration are able to reduce cell viability accompanied by a marked deregulation of activation of pAXL and its downstream pathway (in particular pAKT).

Conclusions: Further investigations are needed to evaluate the combination of anti-proliferative and pro-apoptotic effect of refametinib and axitinib in CRC cell lines.

Legal entity responsible for the study: Department of Clinical and Experimental Medicine ‘F. Magrassi’, Second University of Naples

Funding: Department of Clinical and Experimental Medicine ‘F. Magrassi’, Second University of Naples

Disclosure: All authors have declared no conflicts of interest.
has been shown to increase breast cancer risk in postmenopausal women. Our objective has been to estimate the risk of cancer arising from the common polymorphism within the 5′ untranslated region of the leptin gene (−2,548G/A) and Q223R polymorphisms in the LEPR gene, which has been associated with leptin levels, in a Mediterranean population.

Methods: The PREDIMED Study is a multi-center, randomized trial aimed at assessing the effects of the Mediterranean Diet on cardiovascular primary prevention. We analyzed 1,108 participants (404 men and 704 women) high cardiovascular risk subjects (67 ± 6 years) were selected from a Spanish Mediterranean population. Demographic, clinical, biochemical, anthropometric, genetic and lifestyle variables were obtained.

Results: 84 (7.6%) of the 1,108 participants suffered from cancer after a median follow up of 4.8 years. The group of cancer patients showed 42.9% of current or former smokers versus 33.9% in the non cancer participants group (p = 0.003). The prevalence of the −2,548G/A genotypes were: 21.4% GG, 49.7% GA, 28.9% AA (allele frequencies, G = 0.466 and A = 0.534). The prevalence of the Q223R genotypes were: 13.6% QQ, 47.7% QR, 38.7% RR (allele frequencies, Q = 0.375 and R = 0.625). Interestingly, we found a consistent association of the SNP in the leptin gene with lower cancer risk. The lower risk of cancer associated with the A allele remained significant (OR = 2.21; 95% CI, 1.04-4.72) after adjustment for gender, age and tobacco smoking.

Conclusions: The allele A in the polymorphism −2,548G/A of the leptin gene is associated with lower risk cancer in this Mediterranean population.

Clinical trial identifier: ISRCTN5759639

Legal entity responsible for the study: Universitat de València

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Disclosure: All authors have declared no conflicts of interest.

SGP

Radiotherapy-induced apoptotic tumor cells stimulate proliferation of living tumor cells via caspase 3/7–PKCδ–Akt/p38 MAPK pathway

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Background: Our previous studies demonstrated that radiotherapy-induced apoptotic cells significantly stimulate the proliferation of surviving tumor cells through the caspase 3-FLIP-L-AA-PGE2 pathway. However, the molecular events involved in this stimulation seem to involve in different pathways. This study seeks to investigate the molecular mechanisms involved in the stimulatory role of apoptotic human pancreatic (Panc1) and colonic cancer (HT29) cells in vitro.

Methods: Apoptotic Panc1 and HT29 cells were produced as feeders by 10Gy X-ray radiation. Caspase 3, 7, PKCδ, Akt, p38 MAPK and INK1/2 activation was detected by Western blot. Panc1 and HT29 cells stably transduced by firefly luciferase and green fluorescent protein fusion gene (Panc1-Fluc and HT29-Fluc) were used as reporter. Living Panc1-Fluc and HT29-Fluc cells proliferation on irradiated Panc1 and HT29 cells were evaluated by luciferase activity using bioluminescence imaging.

Results: The presence of apoptotic Panc1 and HT29 cells significantly stimulated the proliferation of living Panc1-Fluc and HT29-Fluc cells. These apoptotic tumor cells showed significantly increased caspase 3 and 7 as well as PKCδ activity. However, significant decrease of the stimulation effect on living Panc1-Fluc and HT29-Fluc cells was observed when apoptotic Panc1 and HT29 cells stably transduced by either dominant-negative caspase 3, caspase 7 or PKCδ were used as feeders instead, and pan PKC δ inhibitor and specific PKCδ inhibitor significantly inhibited the stimulatory effect of apoptotic Panc1 and HT29 cells. Additionally, significantly increased phosphorylation of Akt, p38 MAPK and INK1/2 were observed in the irradiated Panc1 and HT29 cells. Interestingly, dominant-negative PKCδ was resistant to the cleavage and activation by caspase 3 or 7 and the expression of dominant-negative PKCδ attenuated radiation induced Akt phosphorylation in both Panc1 and HT29 cells, attenuated p38 MAPK activation in Panc1 cells.

Conclusions: Apoptotic tumor cells can significantly stimulate the proliferation of living tumor cells through the caspase 3/7–PKCδ-Akt/p38 MAPK pathway after radiotherapy.

Legal entity responsible for the study: Qian Huang, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine

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Disclosure: All authors have declared no conflicts of interest.

SGP

Antitumor immunity against hCGβ induced by a tumor cell vaccine modified with a fusion gene of hCGβ and polyarginines

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Background: Human chorionic gonadotropin β (hCGβ) is a kind of pregnancy hormones, moreover, it is a tumor-associated antigen and also expressed on a variety of human non-trophoblastic tissues such as pancreatic cancer, bladder cancer and lung cancer. Therefore, hCGβ is considered as an ideal target antigen. However, as a self-antigen, hCGβ is tolerated by the immune system and immune response is hardly induced. 9-mer of L-arginine (Arg9), a type of cell penetrating peptide, can play an important role in the translocation process.

Methods: Firstly, we designed and constructed the tumor cell vaccine modified with hCGβ-Arg9 gene and demonstrated that this vaccine can induce cellular immunity, rather than humoral immunity, may play the major role in the antitumor activity.

Results: The transfectant with highest expression of hCGβ was screened and named B16.E5 as a tumor model in this experiment. The results of protective experiment showed B16.E5 cell line expressing hCGβ was acquired by transfected B16.E5 cells with pcDNA3 and selected with G418. Meanwhile we constructed hCGβ-Arg9 gene modified tumor cell vaccine by transient transfection of pcDNA3-Arg9 into B16.E5 cells with liposome. Finally, we took the prophylactic vaccination experiment in vivo to investigate the protective efficacy and the immune mechanisms.

Results: The transfectant with highest expression of hCGβ was screened and named B16.E5 as a tumor model in this experiment. The results of protective experiment demonstrated 60% mice of hCGβ-Arg9 group were protected from the challenge of B16. E5 cells. Moreover, survival benefit was also observed in mice vaccinated with hCGβ-Arg9 tumor vaccine (48 ± 4.5 days). To further explore the experiments for immune mechanism were conducted, including T lymphocytes adoptive transfer experiment, CTL-mediated cytotoxicity analysis, hCGβ antibody tests of serum after vaccination and serum transfer analysis. All of these suggested cellular immunity, rather than humoral immunity, may play the major role in the antitumor activity.

Conclusions: We designed and constructed the tumor cell vaccine modified with hCGβ-Arg9 gene and demonstrated that this vaccine can induce cellular immunity, through which the vaccine can play protective efficacy in animal experiments. Our work may contribute to designing novel generation of tumor vaccines.

Legal entity responsible for the study: Department of Thoracic Oncology, Cancer Center, State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu, China

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Disclosure: All authors have declared no conflicts of interest.

SGP

Association of IFNγ production and NK cytotoxicity in PBL of breast cancer patients

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Background: New insights revealed a critical role for endogenously produced IFNγ in promoting host responses to tumors. In this sense, molecular mechanisms underlying immune dysfunction that include the role of IFNγ in immune responses are not clearly defined in breast cancer.

Methods: PBL of breast cancer patients and healthy controls were analyzed for IFNγ expression and NK cell activity using flow cytometry and 51Cr-release assay, respectively.

Results: Patients in early clinical stage of breast cancer had significantly decreased NK cell cytotoxicity compared to controls. However, patients with advanced clinical stage had significantly decreased NK cell cytotoxicity compared to early breast cancer patients and controls. Positive correlation was shown between intracellular level of IFNγ in PBL and NK cell activity and all investigated patients. However, in patients with advanced disease stage positive correlation between intracellular IFNγ level in PBL and NK cell activity was found, while there was no correlation between the IFNγ level in PBL and NK cell activity in patients in early disease stage. IL-2 increased NK cell cytotoxicity in breast cancer patients and control. Furthermore, IFNγ showed this effect also in patients and controls.

Conclusions: In this study we show that, in breast cancer patients, lower IFNγ level and reduced NK cell cytotoxicity, important in the control of tumor growth, are associated with tumor progression. These results indicate that IFNγ level and NK cell cytotoxicity may represent possible targets in designing new therapeutic agents in this disease.

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Funding: Ministry of Science

Disclosure: All authors have declared no conflicts of interest.
412P The gelatinases-stimuli nanoparticles reverse docetaxel resistance and epithelial to mesenchymal transition in lung cancer cell line

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Background: Drug resistance is a main obstacle for the successful cancer therapy. Emerging evidence suggests that miR-200c functions as an effective cancer stem cells (CSCs) inhibitor and restores sensitivity to microtubule-targeting drugs.

Methods: In the present work, we engineered the intelligent gelatinases-stimuli nanoparticles (NPs) to co-delivery miR-200c and antitumor drug docetaxel (DOC) to verify their synergetic effects on inhibition of CSCs and cancer cells. After tumor cells were treated with miR-200c NPs, miR-200c and its targeted gene class III beta-tubulin (TUBB3) expression were evaluated. The effects of (miR-200c + DOC) NPs on CSC-resistant lung cancer cells viability as well as the expression of E-cadherin and CD44 were studied.

Results: We found that the (miR-200c + DOC) NPs significantly overcome DOC resistance, possibly through elevation miR-200c expression, lower TUBB3 level, and reversed the EMT through upregulation E-cadherin and inhibition lung CSCs.

Conclusions: The (miR-200c + DOC) NPs may provide a new modality for co-delivery of nucleic acid and drugs to inhibit CSCs and reverse drug resistance.

Legal entity responsible for the study: Qin Liu

Funding: The National Nature Science Foundation of China (#1302053)

Disclosure: All authors have declared no conflicts of interest.

420P A novel and unanticipated link between the Werner syndrome protein (WRN) and protein translation

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Background: Loss-of-function of WRN is the cause of Werner Syndrome (WS), a rare autosomal recessive and progressive genetic disorder, which is the responsible of the premature aging in young adults and accompanied by age-related diseases such as rare forms of cancer and type 2 diabetes. WRN is a nuclear protein that play a role in many DNA processes, however its action in cells is poorly understood. Previously we demonstrate that downregulation of WRN induces a metabolic shift that compromises red homoeostasis and limits cancer cell proliferation due to a dysregulation of metabolic proteins, independently of gene expression. Here, we present our preliminary data showing that a small fraction of WRN localize with translational machinery and its absence alter the proper function of this metabolic pathway.

Methods: Depletion of WRN in Hela cells was carry out by a conditional lentivirus machinery and its absence alter the proper function of this metabolic pathway.

Results: We found that the (miR-200c + DOC) NPs significantly overcome DOC resistance, possibly through elevation miR-200c expression, lower TUBB3 level, and reversed the EMT through upregulation E-cadherin and inhibition lung CSCs.

Conclusions: The (miR-200c + DOC) NPs may provide a new modality for co-delivery of nucleic acid and drugs to inhibit CSCs and reverse drug resistance.

Legal entity responsible for the study: Qin Liu

Funding: The National Nature Science Foundation of China (#1302053)

Disclosure: All authors have declared no conflicts of interest.
Abstracts

**Oncoguide system - A computerized self-learning interactive assistance system for the diagnosis and treatment of CML / MPN and MDS**

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**Background:** Clinical practice guidelines (CPG) represent the current state of research. Usually they are passive diseminations (e.g. via print media), but this doesn’t assist the physician in the adaptation of CPG into the daily diagnostic and treatment algorithm to the given boundary conditions (patient, equipment, medical experience). The project aims to develop and implement a computerized interactive assistance system for the diagnosis and treatment of CML / MPN and MDS.

**Methods:** To create the system experts from the medical and the technical domains were necessary. They developed a CPG model in the form of a Unified Modeling Language (UML) activity followed by translation of UML activities into Bayesian nets. The future system is planned to be self-learning by weighing the decision criteria. The knowledge-based system is implemented as a client-server architecture. The server acts as a central data storage in the form of a database. As a client, for example, Internet browsers can be used. The knowledge of guidelines and interviews with experts have to be formalized in an appropriate manner. There are approaches based on an ontological or logic-based modeling. The underlying methodology is based on approaches from artificial intelligence, such as the Bayesian inference or machine learning methods.

**Results:** On the client’s side the system suggests the user appropriate decisions for the diagnosis and treatment. Furthermore, the system can be actively supported by the physician in the adaptation of CPG into the daily diagnostic and treatment algorithm to the given boundary conditions (patient, equipment, medical experience) and has self learning components.

**Conclusions:** The presented computerized interactive assistance system could help to increase the accuracy of diagnosis, treatment and follow up of CML/MPN and MDS.

**Proteomics-based system biology analyses unravel a functional structure with prognostic value**

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**Background:** Urothelial cancer has been traditionally classified based on histology features. Recently, some works have proposed a molecular classification of muscle-invasive urothelial carcinoma (MUC) into basal and luminal subtypes. We aimed to define molecular subtypes of MUC and evaluate the status of several biological processes in the tumor tissue and address its clinical value.

**Methods:** Tissue samples were obtained from 57 pts who underwent curative surgical resection at “Universitary Hospital 12 October” between 2006/12. We analyzed the proteome applying a high-throughput proteomics approach to routinely archive FFPE tumor tissue. Tryptic digests were analyzed by mass spectrometry for protein identification using a Q-Exactive mass spectrometer. Subgroups were defined by hierarchical clustering and random forest. Functional structure was developed using probabilistic graphical models with local minimum Bayesian Information Criterion and Gene Ontology Analysis. Data analysis was done using MeV, BRBArrayTools, R and Cytoscape software suites and Uniprot (http://www.uniprot.org/) and DAVID (http://david.abcc.nig.ac.jp/) webtools.

**Results:** We identified two different molecular subgroups with differential prognosis. Systems biology analyses showed that wide protein expression assessment allows building a functional structure where several nodes with defined biological activity were defined. Activity measurement for each node showed differences between two subtypes in metabolism, focal adhesion, RNA splicing and splicing nodes. Subtypes defined by protein expression are comparable to basal and luminal subtypes defined by gene expression. Moreover, the focal adhesion node has prognostic value in the whole population, and this prognostic information is independent from a predefined prognostic signature (submitted Abstract: Proteomics profile profiling predicts poor prognosis in patients with muscle invasive urothelial carcinoma).

**Conclusions:** Protein data analysis using random forest showed subgroups matching with basal and luminal subtypes obtained by hierarchical cluster analysis. Importantly, we were able to establish different nodes according to biological functions, with diagnostic and prognostic value.

**Legal entity responsible for the study:** Research Institute i + 12

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**Effect of newly synthesized progesteron derivatives on apoptotic and metastatic pathway in MCF-7 breast cancer cells**

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**Background:** Breast cancer is the second leading cause of mortality among women worldwide. Anticancer agents consisting of hybrid molecules are used to improve efficacy and reduce drug resistance. Alteration of different genes is involved in the development of cancer. Consequently, novel anticancer drugs with increased selectivity and specificity are required to overcome limitation of current drugs. A variety of synthetic steroid derivatives have been contrived, most these derivatives can interact with the steroid receptors because of a similarity of shape. Also, the investigation of modified steroid derivatives condensed with various heterocyclic rings has a great attention. Impaired apoptosis and metastasis are critical in cancer development and is a major barrier to effective treatment.

**Methods:** Several progesterone derivatives were synthesized. The structure of the newly synthesized was elucidated and confirmed using the analytical and spectral data. The newly synthesized progesterone derivatives, compounds 1, 2, 3, 4, 5, 6, and 7 were tested for their cytotoxic effects against human breast cancer cells (MCF-7) using neutral red uptake assay. Using QRT-PCR (Quantitative real-time polymerase chain reaction), the expression levels of P53, P21, Cdc2, Bcl-2, Survivin, CCND1, VEGF, HIF-1α, FGF-1, MMP-2, MMP-9, Ang-1 and Ang-2 genes were investigated.

**Results:** All tested compounds showed low IC50 values that were comparable to that of tamoxifen. The most active compounds against MCF-7 cancer cell line was in the descending order of 5 > 1 > 3 > 2 > 4 > 7 > 6. The study revealed that all newly synthesized compounds down-regulated the expression levels of BCL-2, survivin, VEGF, Ang-2 and Mmp-9. Compound 2 down regulated CCND1 gene expression, nevertheless, this was only significant in case of compounds 2, 3, and 6. However, P53 was up-regulated by compounds 3. Moreover, compound 1 significantly down regulated MMP-2, Compounds 3 and 7 significantly down regulated FGF-1.
Results: The control group exhibits a gradual increase in cell proliferation in stromal cells over a 96 hour time course. The CMPOGC & CMPAGC enhances cell growth in stromal cells. In the absence of granulosa cells, CMSC substantially inhibits the growth of the stromal cell population. Western blot on stromal cell lysates was performed for analyzing its treatment responses to conditioned media CMSC, CMPPGC, CMPFGC, CMPOG, CMPOE, and CMPOF. The treatment effects on cell proliferation were analyzed with WST-1 assay. Activation of thyroid gland was observed 1 week after melanoma transplantation: T4 increased by 1.3 times and TSH increased by 1.5 times. T4 and TSH level was still low. In males T4 decreased by 37 times, T3 by 2.1 times, and TSH by 1.7 times. In females T3 by 3.3 times and TSH by 1.4 times lower than the norm. Males showed decrease in levels of both total (by 1.5 times) and free (by 3.3 times) forms with normal TSH content. Significance of the revealed characteristics of melanoma development was proved as correction of the status in females was possible using 1,3-dihydroxybenzimidazole trioxide. As a result, life span increased by 30%, complete tumor regression and recovery with preservation of reproductive function were observed in several cases. Profound thyroid hypofunction could not be corrected in males.

Conclusions: Gender differences were revealed in thyroid gland functioning in dynamics of melanoma development which included profound thyroid hypofunction with the loss of control by the pituitary gland in males and normal production of total forms with a decrease of free forms of the hormone in females. These differences can be taken into account in personalized coonstant treatments.

Legal entity responsible for the study: Rostov Research Institute of Oncology

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A potential natural inhibitor in the autocrine regulation among ovarian stromal cell population & its translational implications

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Background: The ovarian microenvironment is influential on ovarian cancer progression and metastases as it offers a niche of pro inflammatory markers potentiating angiogenesis, growth and tumour progression. We sought to investigate the malleable nature of stromal cells analysing the paracrine communication with granulosa cells and its autocrine regulation in stromal cells using conditioned medium studies.

Methods: Primary stromal cells were cultured from wild type mice C57BL/6. Cultured stromal cells were treated with conditioned media from stromal cells (CMSC), conditioned media of preantral granulosa cells (CMPPGC) and conditioned media of ovarian explants (CMPOE). The treatment effects on cell proliferation were analyzed with WST-1 assay. Western blot on stromal cell lysates was performed for analyzing its treatment responses to conditioned media CMSC, CMPPGC, CMPFGC, CMPOG, CMPOE, and CMPOF. The results are shown in Figure 1.

Results: The control group exhibits a gradual increase in cell proliferation in stromal cells over a 96 hour time course. The CMPOGC & CMPAGC enhances cell growth in stromal cells. In the absence of granulosa cells, CMSC substantially inhibits the growth of the stromal cell population. Western blot on stromal cell lysates was performed for analyzing its treatment responses to conditioned media CMSC, CMPPGC, CMPFGC, CMPOG, CMPOE, and CMPOF. The treatment effects on cell proliferation were analyzed with WST-1 assay. Activation of thyroid gland was observed 1 week after melanoma transplantation: T4 increased by 1.3 times and TSH increased by 1.5 times. T4 and TSH level was still low. In males T4 decreased by 37 times, T3 by 2.1 times, and TSH by 1.7 times. In females T3 by 3.3 times and TSH by 1.4 times lower than the norm. Males showed decrease in levels of both total (by 1.5 times) and free (by 3.3 times) forms with normal TSH content. Significance of the revealed characteristics of melanoma development was proved as correction of the status in females was possible using 1,3-dihydroxybenzimidazole trioxide. As a result, life span increased by 30%, complete tumor regression and recovery with preservation of reproductive function were observed in several cases. Profound thyroid hypofunction could not be corrected in males.

Conclusions: Gender differences were revealed in thyroid gland functioning in dynamics of melanoma development which included profound thyroid hypofunction with the loss of control by the pituitary gland in males and normal production of total forms with a decrease of free forms of the hormone in females. These differences can be taken into account in personalized coonstant treatments.

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Disclosure: All authors have declared no conflicts of interest.
Results: Using IHC, we demonstrated that 4F2hc is aberrantly expressed in PDAC and matched adjacent tissue. However, there was no significant difference in 4F2hc expression in the different grades and stages. Although Kaplan-Meier survival curves and Cox analyses did not reveal a significant association between 4F2hc expression and OS, we observed a trend that suggests an association between absence of 4F2hc expression and prolonged survival. Additionally, our results showed that 4F2hc+ cells isolated from fresh tumor tissue co-expressed other known markers of PDAC such as MUC4 and MUC1. To determine the role of 4F2hc in PDAC, cell behavior between 4F2hc+ cells and 4F2hc low expressing cells was compared. We found that 4F2hc downregulation significantly inhibited tumorsphere formation and cell proliferation by arresting cell cycle.

Conclusions: Herein, we demonstrated that 4F2hc is overexpressed in resected tumor tissue as well as in matched adjacent tissue of patients with pancreatic cancer. Moreover, our data suggests that 4F2hc expression increases tumorigenesis by enhancing cell proliferation and promoting anchorage-independent growth in vitro. Although further studies are needed, our results suggest that 4F2hc might be a novel therapeutic target of PDAC.

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Marine-derived bioactive compound MB-E5 as a cytotoxic agent in glioblastoma cell lines

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Background: Glioblastoma multiforme (GBM) is the most common primary central nervous system tumor. Even with standard and aggressive treatment strategies the 5-year survival rate is less than 30%. Also, previous results reveal that glutathione S-transferase M3 (GSTM3) is highly expressed in brain tissue and represents the predominant activity of GSTs, a group of enzymes that mainly facilitates detoxification, in the human brain. The compound studied here, MB-E5, is extracted from cultured Vibrio psychroerythrus, a marine bacterial species.

Methods: In this study, the cytotoxic activity of MB-E5 in U87MG and GBM8401 glioblastoma cell lines were investigated using MTT assay and TUNEL assay. Tumor sphere assay were performed to determine the impact of MB-E5 on in vitro neuron cancer stem cell growth. Immunofluorescence assay and western blotting were used to evaluate the level of autophagy-related proteins and the PI3K/Akt pathway. gstm3 gene expression levels were measured in TMZ-resistant glioblastoma cell line by semi-quantitative polymerase chain reaction (PCR).

Results: MTT assays show that MB-E5 exhibits higher cytotoxic activity than Temozolomide (TMZ), a first-line drug in the treatment of gliomas, in GBM cell lines. Neurosphere formation is significantly reduced at low MB-E5 levels. TUNEL assay and western blot analysis show that MB-E5 induces apoptosis and reduces glioblastoma cell survival rate by inhibiting the PI3K/AKT/mTOR signaling pathway. Also, immunofluorescence assay and western blotting results indicate that MB-E5 promotes the expression of autophagy marker LC3-II. Furthermore, MB-E5 demonstrates higher cytotoxicity against TMZ resistant-GBM8401 cells. The results of semi-quantitative PCR indicate a decrease in the expression of gstm3 after 3 days of 200 µM TMZ treatment, but the expression level recovers after 15 days of continuous TMZ treatment in the survival population of GBM cell lines. Moreover, GSTM3 mRNA expression is reduced after MB-E5 treatment.

Conclusions: These results suggest that the marine-derived bioactive compound MB-E5 may be effective as a cancer therapeutic agent in glioblastoma. We also theorize that MB-E5 may reduce gstm3, which could play a key role in TMZ-resistant glioblastoma cells.

Legal entity responsible for the study: Doctoral Degree Program in Marine Biotechnology, National Sun Yat-sen University, Taiwan

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Disclosure: All authors have declared no conflicts of interest.
Assessment and comparison of tumor mutational burden and microsatellite instability status in >40,000 cancer genomes

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Background: The overall quantity of mutations in a cancer genome, termed tumor mutational burden (TMB), is an emerging biomarker for response to immunotherapy. Mutations occur in cancer genomes by a number of different processes, each of which is associated with a distinct mutational signature. Microsatellite instability (MSI) is one common mechanism by which cancer cells can acquire high TMB. We sought to explore the relationship of TMB and MSI in a large cohort of advanced cancer cases from a wide array of tumor types.

Methods: CGP targeting >500x sequencing coverage (non-PCR duplicate reads) for the full coding regions of 315 genes was performed on >40,000 cancer specimens from a wide array of tumor types. MSI status was determined by assessing the indel alterations occurring at 114 microsatellites covered by the CGP test. TMB was determined by evaluating the number of somatic, coding, base substitution and indel mutations occurring per megabase of coding genome targeted on the test.

Results: Overall, 1.4% of cases were found to be MSI-High while 7.1% of cases had high TMB. The vast majority (85%) of MSI-High cases also had high TMB, but the converse was not true. Numerous cases with high TMB were observed that did not show evidence of MSI. These results were highly disease specific. In some tumor types very few high TMB cases (<5%) were MSI-High, notably lung, skin, and urinary cancers. On the other hand in gastrointestinal, ovarian, and endometrial cancers the majority of high TMB cases (>75%) were MSI-High. In all tumor types, there was a meaningful fraction of cases with high TMB and no evidence of MSI. The full landscape of TMB and MSI across 40,000 cases and hundreds of cancer sub-types will be presented.

Conclusions: As expected, these results support the understanding that TMB and MSI status in cancer genomes are correlated and that the majority of MSI-High cases also had high overall TMB. These data also demonstrate that a large portion of cancers with high TMB are microsatellite stable. This indicates that assessment of both TMB and MSI will be valuable for identifying patients most likely to benefit from immunotherapy.

Legal entity responsible for the study: Foundation Medicine

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Copy number alterations as predictive biomarkers for response to bevacizumab in metastatic colorectal cancer

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Background: Bevacizumab (BeV) is an angiogenesis inhibitor that is currently used in patients with metastatic colorectal cancer (mCRC). However, response on treatment is variable and predictive biomarkers are urgently needed. The aim of this study was to identify copy number alterations that are associated with response to bevacizumab.

Methods: Within the AngioPredict project tumor tissue samples from 182 mCRC patients treated with chemotherapy alone or chemotherapy plus BeV were retrospectively collected. The overall median progression-free survival (PFS) was 217 days. A second series of 103 patients who were treated with chemotherapy and BeV in the context of the CAIRO2 trial were included for validation purposes. Copy number data, obtained by next generation sequencing (NGS), were analyzed using a routine pipeline, generating regions called for gains or losses. A log-rank test using 10,000 permutations was performed to calculate the significance of DNA copy number correlations to PFS in each study arm. Then Kaplan-Meier analysis was performed for individual candidate regions.

Results: Out of 182 patients in the AngioPredict cohort, after quality assurance checks 157 cases remained for downstream analysis. Out of these 157 patients, 113 patients were treated with chemotherapy in combination with BeV and 44 were treated with chemotherapy alone (non-BeV). Frequency plots for copy number alterations matched with CRC profiles known from literature. Log-rank test revealed significant association between copy number alterations and PFS in the BeV group (P = 0.002), but not in the non-BeV group. The predictive value of loss at chromosome 18q12.1.1-18q12.31 was confirmed in the CAIRO2 validation set.

Conclusions: NGS copy number sequencing revealed that loss of chromosome 18q12.1.1-18q12.31 is associated with prolonged PFS in patients treated with chemotherapy plus BeV and may serve as a candidate biomarker for response to BeV. Further studies are needed to confirm these results.

Multidisciplinary molecular tumour board: a tool to improve clinical practice and selection accrual for clinical trials in cancer patients

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Background: Personalized medicine, based on the discovery of druggable targets through Next-Generation Sequencing (NGS) and other molecular profiling techniques, is changing the clinical practice in Oncology. In this setting, Molecular Tumour Board (MTB) became a crucial multidisciplinary tool for results interpretation in order to better select the treatment for our patients, including the inclusion in clinical trials.

Methods: We analysed, retrospectively, a cohort of patients with several advanced solid tumours and no candidate for standard treatment consulted in Phase I – Early Clinical Trials Unit of the Antwerp University Hospital with molecular profile (MP) that were discussed in the MTB. Patients with in house and commercial NGS platforms were included. A subgroup of those patients were analysed also based in immunohistochemistry (IHC) and/or in situ hybridization (ISH).

Results: In this study, 141 tissue samples of 133 national and international patients were included. The median age was 59 years old (18 – 85). The majority of the patients were women (56%). A total of 77.9% of patients (n = 107) had genomic alterations with an average of 3.44 alterations; of which 80.4% (n = 86) correspond to gene mutations in a panel. In this group, the most common alterations were: TOPO1 (9%), TOP2A (9%), MGMT (8%), KRAS (13%), PIK3CA (9%) and APC (7%) were the more frequent mutated genes. In the subgroup analysis of patients with additional MP information (IHC = X; CISH = 4; FISH = 6) the more common alterations were: TOPO1 (9%), TOP2A (9%), MGMT (8%), KRAS (13%), PIK3CA (9%) and APC (7%) were the more frequent mutated genes. In the subgroup analysis of patients with additional MP information (IHC = X; CISH = 4; FISH = 6) the more common alterations were: TOPO1 (9%), TOP2A (9%), MGMT (8%), KRAS (13%), PIK3CA (9%) and APC (7%) were the more frequent mutated genes. In the subgroup analysis of patients with additional MP information (IHC = X; CISH = 4; FISH = 6) the more common alterations were: TOPO1 (9%), TOP2A (9%), MGMT (8%), KRAS (13%), PIK3CA (9%) and APC (7%) were the more frequent mutated genes.

Conclusions: The MTB became a crucial multidisciplinary tool for results interpretation in order to better select the treatment for our patients, including the inclusion in clinical trials.


Legal entity responsible for the study: VU University Medical Center

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Extended genotyping of RAS/BRAF for improved selection of metastatic CRC patients to anti-EGF therapy: Comparison of three platforms


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Background: The significance of low-frequent RAS pathway mutated alleles and the optimal sensitivity cut-off in the prediction of response to anti-EGF therapy in metastatic colorectal cancer (mCRC) patients remains controversial. We aimed to evaluate the added value of RAS panel using both commercial assays (Roche Cobas® and QiaGen Therscreen® pyrosequencing kit) and a highly-sensitive and quantitative digital FCR (dPCR).

Methods: Analysis of hotspot including RAS (KRAS + NRAS ex 2/3/4) and BRAF (ex 15) mutations translated into a higher RR (Table). PFS/OS were significantly associated with lack of mutations in RAS and BRAF (yes/no) and radiologic response was observed (p < 0.001). Likelihood ratio analysis showed that 1% or higher of any mutated alleles offered the best predictive value for all combinations of RAS/BRAF analysis. The overall RR was 32.3% and analysis of mutations translated into a higher RR (Table). PFS/OS were significantly associated with lack of mutations in RAS and BRAF (Table). However, the predictability of both RAS/BRAF and OS was higher in the first-line setting when we considered a threshold of 1% in RAS/BRAF scenario (HR = 2.03; CI95% [1.2-3.43], p = 0.008 for PFS, and HR = 1.95; CI95% [1.09-3.48], p = 0.024 for OS). No differences in PFS or OS was bevacizumab group were observed by molecular profiling with any platform.
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Conclusions: RAS and BRAF mutational analysis improved prediction of response to anti-EGFR therapy. Additionally, dPCR with a threshold of 1% outperformed the other platforms in first-line setting.

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MHC class II in lung cancer


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Background: Immune therapy is a recent hotspot in lung cancer research. The ability of the immune system to recognize tumor cells as foreign is restricted through the expression of certain cell-surface molecules such as the major histocompatibility complex (MHC) molecules. The alteration in MHC class II antigens is an event that occurs frequently on primary and metastatic cancer. Therefore, we described the expression of MHC class II in lung cancer cell lines and patient tissues.

Methods: We studied MHC II (DP, DQ, DR) (CR3/43, Abcam) protein expression in 55 non-small cell lung cancer (NSCLC) cell lines, 42 small cell lung cancer (SCLC) cell lines and 278 lung cancer patient tissues by immunohistochemistry (IHC).

Results: Seven (12.7%) NSCLC cell lines were positive for MHC class II. No SCLC cell lines were found to be MHC II positive. MHC class II was detected in 139 lung cancer samples from the Hirsch Lab. Twenty-one (31.3%) samples stained positive for MHC class II on tumor cells, and 38 (58.6%) had positive MHC class II expression on tumor infiltration lymphocytes (TILs) in NSCLC. There was no positive MHC class II staining on SCLC tumor cells. MHC class II on TILs in NSCLC was significant lower than MHC II on TILs in NSCLC (P = 0.001). MHC class II was detected in 139 NSCLC tumor tissues from Medical University of Gdańsk. Forty-two samples (30.2%) stained positive for MHC class II on tumor cells, and 55 (39.6%) had positive MHC class II expression on TILs in NSCLC. MHC class II on tumor cells was expressed less in non adenocarcinoma compared to adenocarcinoma (P = 0.002). MHC class II on TILs had higher expression in stage I and II compared to stage III and IV NSCLC (P = 0.027). High expression of MHC class II on tumor cells was correlated with high expression of MHC class II on TILs (P = 0.023). Positive staining of MHC class II on TILs had longer RFS and OS than patients who were MHC II negative on TILs (1.05 years 95% CI 0.57-1.55 vs. 2.98 years 95% CI 1.63-4.33, P = 0.028) (1.39 years, 95% CI 0.63-2.15 vs. 3.23 years 95% CI 2.62-3.84, P = 0.014).

Conclusions: MHC class II was expressed in both NSCLC cell lines and tissues. However, MHC class II was absent in SCLC cell lines and tissue tumor cells. Loss of expression of MHC II on SCLC tumor cells may be a means of escaping anti-cancer immunity. MHC class II expression on TILs correlated with good prognosis in NSCLC patients.

Clinical trial identification: N/A

Legal entity responsible for the study: Yuli He

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Th1 epitopes as potential biomarkers for ipilimumab treatment


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Background: Ipilimumab may unleash T cells in many tumors and effectively be combined with multi-antigen vaccines. The unleashed T cells could be detrimental if they are the wrong phenotype such as Th2. Th1 peptides from 4 proteins associated with Th1 response were used for ELISPOT assay was performed using 13 Th1 epitopes. Patients with predominant either Th1 (n = 11) and Th2 (n = 28) response were treated with 25-50 mg of total ipilimumab weekly for three weeks before starting standard of care treatment. Th1 epitopes from EGF (4), Bcl-2 (3), Survivin (5) and Sox2 (3) were used for ELISPOT studies.

Results: Th1 peptide-specific immune responses against at least one Th1 epitope of each protein had better clinical responses with ipilimumab treatment in comparison with the Th2 patients (p = 0.001). Th1 responders pre-treated with ipilimumab before standard of care treatment had overall survival (OS) of 2 yrs for ovarian, 2.3 years for CRC, 1.8 years for MM, 2.6 years for TNBC and 8 months for pancreatic cancer. The Th2 responders had OS of less than 6 months in average.

Conclusions: Patients with pre-existing Th1 response had a better prognosis and better overall survival in comparison with Th2. This could explain why pseudoprogressions seen in patients treated with checkpoint inhibitors could be in fact progression disease due to the unleash of Th2 cells, which are associated in the majority of the tumors with bad prognosis and tumor progression. Antigen-specific immune response against Th1 epitopes from four bad prognosis proteins may serve as biomarker to treat multiple tumors with ipilimumab.

Legal entity responsible for the study: Centro De Investigacion Del Cancer En Sonora

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Disclosure: All authors have declared no conflicts of interest.

SOP

Genomic alterations in circulating tumor DNA (ctDNA) are associated with clinical outcomes in treatment-naive metastatic castration-resistant prostate cancer (mCRPC) patients commencing androgen receptor (AR)-targeted therapy


Background: There are no established genomic biomarkers to predict response to the AR-targeted therapies enzalutamide and abiraterone, partly due to the impracticality of sampling tissue in a bone predominant metastatic disease. Cell-free DNA (ctDNA) is a promising “liquid biopsy” approach to genomic characterization of mCRPC.

Methods: We performed deep targeted sequencing of 72 mCRPC-related genes in baseline ctDNA from 62 chemotherapy-naïve mCRPC patients enrolled in an ongoing randomized phase II trial of abiraterone or enzalutamide (NCT02125357). Genomic alterations in ctDNA were examined for association with clinical variables including time on treatment.

Results: Evidence for ctDNA was detected in 38 of 62 (61.3%) ctDNA samples at baseline with 27 samples harbouring ≥1 mutation(s) with an allele fraction above 1%, and 28 samples containing copy number alterations affecting ≥2 genes. Patients with confirmed ctDNA displayed a trend towards higher ctDNA yield (P = 0.07), higher baseline PSA (P = 0.14), and shorter time on treatment (P = 0.12). AR amplification was found in 17 patients and associated with shorter time on treatment (median 200 vs 420 days, p = 3.5 x 10⁻²). AR mutations were found in 6 patients, exhibited mosaicism with amplifications, and correlated with prior non-steroidal anti-androgen therapy. TP53 and BRCA2 inactivating alterations were detected in 17 and 9 patients respectively and were associated with shorter time on treatment (median 236 vs 420 days, p = 1.1 x 10⁻⁵, median 120 vs 342 days, p = 5.6 x 10⁻⁵, respectively). The associations for AR, TP53 and BRCA2 remained significant after adjusting for patient age, baseline PSA and ctDNA presence (p < 0.005).

Conclusions: In this preliminary analysis, the majority of patients with treatment-naive mCRPC had detectable ctDNA and the presence of certain genomic aberrations was associated with shorter duration of therapy with abiraterone or enzalutamide. ctDNA holds great potential as a minimally-invasive biomarker to identify chemotherapy-naive mCRPC patients that have poor therapeutic outcomes.

Clinical trial identification: NCT02125357

Legal entity responsible for the study: Dr. Alexander Wyatt and Dr. Kim Chi

Funding: Research grants from the Canadian Cancer Society and Prostate Cancer Canada. Academic support from the BC Cancer Foundation and the Vancouver Prostate Centre (UBC), Industry grants from Janssen and Astellas.

Disclosure: S. Parimi: Honoraria from Astellas for a journal club presentation (February 2016) and an advertisement board sponsored by Janssen (April 2016). D. Finch has received honoraria for participation on an ad boards for Janssen and Astellas. Was a PI on the enzalutamide Affirm clinical trial. J. Vergidis: Has received honoraria from Astellas and am a member of an advisory board also for
Circulating free tumour-derived DNA (ctDNA) to detect EGFR mutation in patients (pts) with advanced NSCLC (anNSCLC): French subset analysis of the ASSESS study

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Background: ASSESS (non-interventional diagnostic study NCT01785888) assessed the concordance of EGFR mutation status in tumour samples and plasma ctDNA in pts with anNSCLC in Europe and Japan. Subdata for pts from France are presented.

Methods: Pts: stage IIB/IV chemo-/TKI-naive NSCLC. Primary endpoint: EGFR mutation status concordance between matched plasma and tumour samples. Tumour testing was performed locally as per local practice; plasma testing was centralised. ctDNA was extracted using the PureLink Virus Kit on an iPrep Purification Instrument (Life Technologies) and EGFR mutations detected via the approved Therascreen EGFR RKO Kit (Qiagen).

Results: Of 1311 enrolled pts, 145 were from France (mean age 64 years, 64% male, 83% ever-smokers). Most samples were collected from primary tumours (81%); collection was mostly via bronchoscopy (38%) and image-guided core biopsy (19%). Of the 113 pts EGFR mutation-negative in tissue, one tested plasma-positive; reanalysis via 2 different techniques confirmed the result. Sensitivity of plasma testing was 61.5%. Of the 113 pts EGFR mutation-negative in tissue, 126 were evaluable for EGFR; activating mutations were found in 13 (EGFR mutation frequency 10%). 10 pts tested positive for EGFR mutations detected via the approved Therascreen EGFR RKO kit in plasma.

Conclusions: These real-world data confirm ctDNA as a powerful alternative sample for EGFR mutation analysis in anNSCLC.

Table: 60P Matched tissue/cytology samples (N = 126)

<table>
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<th>% Exact 95% confidence interval</th>
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</tr>
<tr>
<td>Sensitivity</td>
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</tr>
<tr>
<td>Specificity</td>
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</tr>
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<td>88.9</td>
</tr>
<tr>
<td>Negative-predictive value</td>
<td>112/117</td>
<td>95.7</td>
</tr>
</tbody>
</table>

Clinical trial identification: NCT01785888

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca


Frequency and abundance of plasma T790M mutation associated with failure patterns of EGFR-mutant NSCLC treated with tyrosine kinase inhibitors

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Background: T790M mutation is a major mechanism for EGFR-TKI failure. However, few studies explored its correlation with failure patterns and response duration partly due to difficulty in re-biopsy. Droplet digital PCR (ddPCR) is able to detect the frequency and abundance of T790M non-invasively in circulating tumor DNA (ctDNA).

Methods: 314 patients with advanced or recurrent NSCLC who had progressed during EGFR-TKIs treatment were enrolled prospectively (NCT02418234). Blood samples were drawn within two weeks from PD occurred. T790M mutations were both evaluated by ARMS and ddPCR. EGFR-TKIs failures were divided into three patterns, chemotherapy limited (CF, PD due to lesions limited in chest or one distant site), tumor limited (OF, PD due to lesions in one distant site or multiple sites including chest or intracranial). The frequency and abundance of T790M mutations were analyzed for association with failure patterns and disease characteristics.

Results: T790M mutations were detected in 30.9% (97/314) and 46.8% (147/314) patients by ARMS and ddPCR. The median abundance of T790M mutation was 1.2% (0.03% to 70.3%). The overall concordance was 78.3% (246/314) between ARMS and ddPCR. 94.6% (158/167) for ARMST790M+/ddPCRT790M+, and 59.9% for ARMST790M+/ddPCRT790M-. There were 62.4% (196/314), 10.8% (34/314), and 26.8% (84/314) patients in failure patterns of CF, BE, OF, respectively. 25% (49/196), 5.9% (2/34), and 54.8% (46/84) patients with PD patterns of CF, BE, and OF were detected ARMST790M+/ddPCRT790M+ < p < 0.001 as well as 39.8% (78/196), 20.6% (7/34), and 73.8% (62/84) by ddPCR (p < 0.001). The mean T790M abundance of CF, BE, and OF was 1.34%, 0.77%, and 5.07%, respectively (p < 0.001). The median PFS was 12.8 months. No difference of PFS in each failure pattern (13.1/11.2/12.6 months for CF/BE/OF, p = 0.762) and no correlation of PFS was found in patients with different level of T790M mutant abundance in ctDNA (p = 0.33).

Conclusions: Using plasma samples to detect T790M is feasible. Different TKI failure patterns correlated with T790M ctDNA status as well as the mutation abundance. Clinical trial identification: NCT02418234

Legal entity responsible for the study: Hangzhou First People’s Hospital

Funding: Projects of medical and health technology program in Zhejiang province (WKJ-21-1532)

Disclosure: All authors have declared no conflicts of interest.
acquired resistance to EGFR TKIs, all of them had activating EGFR mutations in liquid biopsies (31 L858R, 22 bp deletions in exon 19, 1 G719X, 39 women, 15 males)

Results: Using the iPLEX assay, we had identified 36% (18/54) of T790M. Using UltraSEEK on the same ctDNA samples 50% (27/54) were positive for T790M, increasing by 33% the detection of omatic EGFR T790M in ctDNA samples.

Conclusions: The MassARRAY system with UltraSEEK detects 50% T790M in ctDNA samples concomitantly with EGFR activating mutations in patients whose tumors had developed resistance to EGFR TKIs and could benefit from Osimertinib.

Legal entity responsible for the study: Nippon Medical School

Funding: Research funding of Department of Digestive Surgery, Nippon Medical School

Disclosure: All authors have declared no conflicts of interest.

Liquid biopsy testing in routine clinical management of advanced non-small cell lung cancer: clinical validation in a single biopathology laboratory

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Background: Molecular profiling of cell-free circulating tumor DNA (ctDNA) in patients with advanced NSCLC has become a powerful diagnostic approach for targeted therapy selection and monitoring response. We carried out clinical validation of ctDNA testing as liquid biopsy in patients with advanced NSCLC in ISO15189-accredited biopathology laboratory.

Methods: We performed (i) pre-analytic and analytic validation in comparison with tumor tissue from 270 NSCLC patients; (ii) real-time evaluation of ctDNA analysis for EGFR mutations before anti-EGFR therapy in 16 patients; and (iii) the study of resistance mutations in 34 refractory patients under treatment. For blood collection, EDTA and Cell-Free DNA BCT tubes (Streck) were used. ctDNA was extracted from plasma using the QIAamp Circulating Nucleic Acid Kit (Qiagen). ctDNA mutation status was assessed using (i) the Therascreen EGFR RTQ PCR kit (Qiagen), and (ii) NGS assay interrogating >1800 mutation hotspots in 22 cancer-associated genes using the Oncomine Solid Tumor DNA panel and Ion PGM sequencer (ThermoFisher).

Results: The analytic validation demonstrated 70% sensitivity and 98% specificity for the EGFR RTQ kit with limit-of-detection >1%. ctDNA yield was not affected by storage in Streck BCT tubes >1%. The EGFR RGQ kit with limit-of-detection >5%. 43% of samples were found mutant by the Oncomine Solid Tumor DNA panel and Ion PGM sequencer (ThermoFisher).

Conclusions: The analytic validation demonstrated 70% sensitivity and 98% specificity for the EGFR RTQ kit with limit-of-detection >1%. ctDNA yield was not affected by storage in Streck BCT tubes >1%. The EGFR RGQ kit with limit-of-detection >5%. 43% of samples were found mutant by the Oncomine Solid Tumor DNA panel and Ion PGM sequencer (ThermoFisher).

Correlation of circulating tumor cells with myeloid-derived suppressive cells in the peripheral blood of patients with advanced small cell lung cancer


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Background: The accumulation of Myeloid-derived Suppressor Cells (MDSCs) and the Circulating Tumor Cells (CTCs) have been proposed as negative prognostic biomarkers in several tumors, including SCLC. However, no studies have shown a correlation of the MDSCs with CTCs in SCLC patients. We aimed to investigate the clinical relevance of CTCs and MDSCs in progressing patients with advanced SCLC.

Methods: Peripheral blood was obtained from 32 SCLC patients at the time of progression after 1st line chemotherapy and 11 healthy controls (HC). Immune cells were determined using flow cytometry and CTCs were detected using both the CellSearch System (CS) and immunofluorescence double staining of PBMCs with anti-TTF1 and/or anti-CD56 and anti-CD45 antibodies (IF). The median percentage of patients MDSCs at baseline was used to characterize MDSCs as high or low. For the CTCs detection using the CS and IF, the cut-off values were ≥2 and ≥1 CTCs respectively.

Results: The percentage of naïve CD4+ T cells was decreased in patients vs NC at baseline. The whole population of MDSCs (CD3−Lin+HLA-DR+<5%) as well as the granulocytic (CD15−CD14−CD33−CD11b−) and the monocytic (M)-MDSCs (CD14+CD15−CD33−CD11b−Lin−HLA-DR+<5%) were significantly increased in patients (p < 0.001). Only M-MDSCs levels were significantly correlated with TTF1+ (p < 0.018) but not with CD56+ or TTF1+/CD56+ CTCs. Conversely, there was no correlation of the different MDSCs subtypes with the CTCs detected using the CS. Patients with high M-MDSCs levels had a higher absolute number of TTF1+ CTCs compared to patients with low M-MDSCs levels (Mean: 46 vs 2 cells; p = 0.02) whereas the frequency of M-MDSCs was higher in patients with TTF1− CTCs compared to those with TTF1+ CTCs (mean: 4.6% vs 1.7%; p = 0.01).

Conclusions: We showed an increased frequency of M-MDSs in the blood of patients with SCLC at relapse exhibiting a positive correlation with CTCs. These observations seem to indicate that some CTCs’ subpopulations may be escape and proliferate in patients with active immunosuppressive mechanisms.

Legal entity responsible for the study: N/A

Funding: Laboratory of Translational Oncology, School of Medicine, University of Crete

Disclosure: All authors have declared no conflicts of interest.
Background: Since tissue is not always available, biomarkers testing can be performed on circulating free DNA (cfDNA). Compared to real time PCR, next generation sequencing (NGS) can be narrowed to target a limited number of actionable genes. This strategy, known as ultra-deep sequencing, requires a careful validation. Here we validated a narrowed gene panel to produce a DNA library covering 568 actionable mutations in six gene (EGFR, KRAS, NRAS, BRAF, cKIT and PDGFR).

Methods: This study had a retrospective and prospective design. After In - vitro studies on cell lines aimed to assess the assay analytical performance, cfDNA from a retrospective series of cases included lung (n = 51) and colon (n = 3) neoplasms and melanomas (n = 9) previously well characterized on both tissue and matched cfDNA was employed to validate the SiRe panel. Then, blood samples prospectively collected from NSCLC patients (n = 87) were tested to assess this panel performance in daily clinical practice.

Results: On cell lines, the SiRe had high intra – and inter – run reproducibility with 0.2% lower limit of mutation detection. In the prospective series of cfDNA, a total of 54 mutations were detected by SiRe showing 100% specificity, confirming 39 EGFR, 9 KRAS, 5 BRAF mutations previously detected on matched tissue. Noteworthy, in 4 cases SiRe detected mutations that had been missed on cfDNA by real time PCR. On prospectively collected cfDNA, SiRe detected in 4/46 patients, without baseline tissue availability, activating EGFR mutation, at the time of tumor progression following the treatment with gefitinib, erlotinib and afatinib SiRe detected T790M in 30% (9/30). On the overall, the SiRe panel showed a sensitivity of 93.4% and specificity of 100%. The SiRe panel was an effective tool enabling a cost - effective implementation of NGS for cfDNA mutational profiling in molecular pathology practice.

Conclusions: The SiRe panel is an effective tool enabling a cost - effective implementation of NGS for cfDNA mutational profiling in molecular pathology practice.

Legal entity responsible for the study: University of Naples Federico II. Department of Public Health.

Funding: University of Naples Federico II. Department of Public Health.

Disclosure: All authors have declared no conflicts of interest.

External quality assessment of EGFR testing in circulating DNA: a French pilot study

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1Biochemistry, CHU de Nantes, Nantes, France, 2Pathology, Institut Universitaire du Cancer - Toulouse- Hospital, Toulouse, France, 3Oncopharmacology, Centre Paul Popin, Angers, France, 4Oncologie Biologique, CHU Poitiers, Jean Bernard Hospital, Poitiers, France, 5Genetique, CHU de Pontchaillou, Rennes, France, 6Biologie des Tumeurs, CHU Hôpital Haut-Lévêque, Bordeaux, France, 7Bioenergie, CHU Hôpital Haut-Lévêque, Limoges, France, 8Biochimie, CHU Hôpital Trousseau, Tours, France

Background: Tissue testing for NSCLC patients is routinely performed in France in the regional platforms certified by the French National Cancer Institute (INCa). All laboratories participate in an annual EQA scheme for tissue testing, but there is no EQA for circulating tumor DNA testing. Therefore, we set up a pilot study to assess quality testing in western France.

Methods: Artificial samples were prepared by supplementing normal plasma (Clinisciences) with DNA extracted from control FFPE sections (Horizon Diagnostics) or plasma from NSCLC patients. Aliquots (2 ml) of 8 different samples were sent in dry ice. DNA extraction and EGFR testing (exon 19 deletions, L858R, G719X and T790M mutations) were performed according to local practice. Data were collected and compared to the expected results.

Results: We collected 10 complete sets of data from 9 labs. DNA was extracted from 1 ml (n = 4) or 2 ml (n = 6) using the QIAmp circulating DNA kit (Qiagen; n = 3), the Maxwell system (Promega; n = 4) or the ddPCR sample prep (Roche; n = 3). Mutation testing was performed by NGS (n = 4), using the COBAS EGFRv2 kit (Roche; n = 3) or the Therascreen EGFR RQG kit (Qiagen; n = 2), using droplet digital PCR (BioRad; n = 1) or pyrosequencing (Qiagen; n = 1). A single false positive result was observed (T790M detected by NGS). The sensitivity (number of mutations detected / number of mutations present in the set of samples) and the number of correct genotypes are presented on the table. This pilot study suggested that, under the specific conditions of this scheme, the COBAS kit was the most sensitive approach.

Table: 69P

<table>
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<tr>
<th>Lab N°</th>
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<tr>
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<td>5</td>
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<td>62.5% (5/8)</td>
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<td>7</td>
<td>77.8% (7/9)</td>
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<tr>
<td>COBAS EGFR v2</td>
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<td>Therascreen RQG v2</td>
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<td>Pyrosequencing</td>
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</table>

Conclusions: This pilot EQA allowed each lab to evaluate its practice and could be used to improve their process. These information will be important for labs that have not yet decided which technique to use for DNA testing. Samples were simple to prepare and it will be easy to scale-up this process. A similar approach using other genes (BRAF, KRAS and NRAS) will also be developed. Supported by a grant from Astra Zeneca.

Legal entity responsible for the study: N/A

Funding: Astra Zeneca

Disclosure: M.G. Denis: Advisory board Qiagen. All other authors have declared no conflicts of interest.

Diagnostic performance of liquid biopsy for pancreatic solid lesion as alternative to endoscopic ultrasound-guided fine needle aspiration (EUS-FNA)


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Background: EUS-FNA is considered as the reference procedure for the diagnosis of solid pancreatic tumor. Liquid biopsy (CA19.9, circulating tumor cells (CTC)) and
circulating tumor DNA (ctDNA) is an attractive alternative approach. We previously reported that the detection of ctDNA had a diagnostic accuracy of 70% for pancreatic adenocarcinoma (PA) (Am J Gastroenterol 2013;108:152-155). The aim was to evaluate the diagnostic performance of each of these biomarkers (alone or combined) in an extended series of patients with pancreatic solid tumors.

Methods: From 01/2011 to 03/2014, all patients with pancreatic solid tumors diagnosed on CT-scan and referred for a EUS-FNA were included. For each patient, 1 EDTA tube (CTC) and 1 heparinized plasma tube (CA19.9) were systematically collected before EUS-FNA. CTCs isolation was performed using the Screencell® Cyto filtration. CTCs were characterized by an experienced cytopathologist blinded to the histological diagnosis. ctDNA extraction was performed on the remaining heparinised plasma sample if available. CNDA was analysed with QX200™ Droplet Digital™ PCR System (ddPCR) and a multiplex assay allowing screening in a single sample for multiple (n = 7) KRAS mutations (c.34G Â→ A, c.34G Â→ G, c.34G Â→ T, c.34G Â→ A, c.35G Â→ C, c.35G Â→ T and c.34G Â→ A).

Results: A total of 66 patients were included (58 with a malignancy tumor (52 PA and 6 other malignant tumors) and 10 with benign lesion. The stage at diagnosis for PA was localized, locally advanced and metastatic in 13, 17 and 22 patients respectively. Sensitivity (Se) of EUS-FNA performed at inclusion for the PA diagnosis was 65%. Se of CTCs, ctDNA and CA19.9 was 64%, 63% and 79% respectively. Se of each marker increased proportionally with stage (i.e. Se (metastatic PA) = 77%, 85% and 80% for CTCs, ctDNA and CA19.9). Specificity (Sp) of these biomarkers was 81%, 79% and 93% respectively. All 3 biomarkers were available for 51 patients. Positivity of at least 2 on 3 was associated with a Se of 77% and a Sp of 91%.

Conclusions: Our results confirm that CA19.9 alone or in combination with CTCs and/or CNDA represents a non-invasive and effective method as an alternative to EUS-FNA for PA diagnosis.

Legal entity responsible for the study: CHU Rouen

Funding: Association de Cancérologie Digestive de Haute Normandie

Disclosure: All authors have declared no conflicts of interest.

Prospective analysis of CEA, CA19.9, circulating DNA (cDNA) and circulating tumour cells (CTC) in patients (pts) treated for a metastatic colorectal cancer (mCRC). Results of COCA-COLON study

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Background: CEA, CA19.9, cDNA and CTC have been reported as useful circulating markers in mCRC pts treated with chemotherapy (CT)-based regimen. We previously reported that CEA kinetic (threshold 0.05) was associated with outcome (Ann Oncol 2008;19:3681-6). We designed a prospective multicentric trial for CEA kinetic validation and to evaluate CA19.9, cDNA and CTC kinetics.

Methods: mCRC pts, Pts 0-2, with CEA ≥ 5 µg/L or CA19.9 ≥ 30U/mL and who started a CT regimen were included. Plasma were collected taken from baseline (T0) to week 6 (W6) for CEA and CA19.9, and at T0 and T6 for DNA and CTC kinetics. Cell-free DNA (cDNA) was quantified by fluorimetric method, circulating tumour DNA (ctDNA) by digital PCR and CTCs (CTC+) vs (CTC-) by Screencell® method. Primary endpoint was 3-months evaluation (control disease (CD) (response/ stable) vs progressive disease (PD)) (RE CeST 1.1) according to CEA kinetic. Secondary endpoints were progression-free survival (PFS) and overall survival (OS) according to baseline T0 median values (high vs low) of CEA, CA19.9, cDNA, ctDNA, and CTC +/− and kinetics.

Results: A total of 200 mCRC pts were included with a median follow-up of 12 months (range 1-44). Median CEA, CA19.9, cDNA and ctDNA were 96 µg/L, 88 U/mL, 24.2 ng/mL and 15.2% respectively. cDNA was detected in 90% at T0 from the 95 KRAS/BRAF mutated tumours. A total of 54.7% were CTC+ at T0. CEA kinetic (≤0.05 threshold) was associated with response CD (90% vs 52%, p < 0.0001), PFS (8 vs 3.5 months, HR 1.65, p < 0.002). Among other tested kinetics, CA19.9 Kinetic (≥0.12) was associated with PFS (9 vs 5 months, HR 1.5, p = 0.043) without impact on OS. In multivariate analysis model taking account variable tested at baseline, median CA19.9 (Ora 3.81) and median cDNA (Ora 3.48) were independent factor of PD while only median cDNA was independent factor of PFS (Ora 2.3) and OS (Ora 2.1).

Conclusions: This prospective study confirmed that CEA kinetic is clinically relevant to monitor CT in mCRC. Results also highlight that CA19.9, cDNA and ctDNA are also associated with outcome.

Clinical trial identification: Protocol : 2009/170/HF Clinical trial number : NCt01212510

Legal entity responsible for the study: CHU Rouen

Funding: Amgen, Roche and Merck (pharma) Foundation Pierre Durand et Marie-Therese Chevalier

Disclosure: D. Sefrioui, P. Michel, F. Di Fiore: Industrial partnership with Merck, Amgen and Roche. All other authors have declared no conflicts of interest.

Survivin gene expression in the primary tumor and circulating tumor cells – a new biomarker of tumor progression of breast cancer

Y. Shiki et al

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Background: Breast cancer is a leading cause of morbidity and mortality of the female population from malignant tumors. Distant metastases are the main cause of death of patients, a substrate for the development of which are circulating tumor cells (CTCs). However, the search for these cells alone is not sufficient to provide full information about the nature and course of the primary tumor in patients. The search for expression of gene tumor genes responsible for the different processes of tumor progression allows a more complete picture. Such genes include the gene survivin (BIRC5) family of inhibitors of apoptosis (IAP).

Methods: Using real-time PCR we investigated the expression of the survivin gene in 36 samples of primary invasive ductal carcinoma of the breast, 10 samples of benign tumors - fibroadenoma of the breast, as well as 36 samples of peripheral blood of patients with breast cancer at various stages of tumor and stage specific treatment, and 10 healthy people as controls.

Results: In primary breast carcinoma we determined a high expression of survivin gene in all 36 samples with the average value (M ± m) 1.58 ± 0.31 (min – 1.19, max – 4.41). The highest figures were found in tumors of medium and high grade (G II-III) with lymphovenuous invasion (LVI+) . In 2 of 3 samples of benign tumor expression of survivin was not found, and one was 0.015. In CTCs, isolated from peripheral blood of breast cancer patients, all 36 samples as determined by the gene expression of survivin with an average value (M ± m) 1.10 ± 0.19 (min – 0.36, max – 3.79). The level of expression of the control samples did not exceed 0.003. It should be noted that the maximum volume of expression was obtained in samples of tumor patients with stage N+, and especially M1, on TNM classification. Any legitimate expression of survivin, depending on the size of the tumor had been received. In patients, receiving chemotherapy average expression survivin gene was observed, but it never approached the indicators of control.

Conclusions: Determination of expression of the survivin gene in primary tumor and in CTCs may be one of the most promising markers of tumor progression and for monitoring of breast cancer therapy.

Legal entity responsible for the study: Vitebsk State Order of Peoples’ Friendship Medical University

Funding: Belarusian Republican Foundation for Fundamental Research

Disclosure: All authors have declared no conflicts of interest.

Evaluation of PD-1 and PD-L1 expression on CTCs isolated from non-small cell lung cancer (NSCLC) tumor patients

G. Kaiferli1, D. Aggouraki1, P. Katsarlinos1, A. Koutsopoulos2, V. Georgoulias1, A. Kotsakis1

1Laboratory of Translational Oncology, School of Medicine, University of Crete, Heraklion, Greece, 2Department of Pathology, University Hospital of Heraklion, Heraklion, Greece

Background: Lung cancer is the most common cause of cancer related death worldwide. Circulating tumour cells (CTCs) allows the assessment of tumor changes over time. Tumor cells may escape from the immune system through, among others, the PD-1/PD-L1 interaction between tumor cells and immune system which results to immunosuppression. The expression of PD-1/PD-L1 interaction between tumor cells and immune system which results to immunosuppression. The expression of PD-1/PD-L1 on CTCs isolated from NSCLC patients was investigated.

Methods: CTCs were isolated, based on their size, using the Isbt platform from 30 chemo-naive patients with stage IV NSCLC before chemotherapy and after the 3rd cycle. CTCs were detected after staining with Giemsa, as well as after immunofluorescence double staining with Cytokeratin (A45-B/B3)/PD-1 and Cytokeratin (CK)/PD-L1 antibodies and analysis with the ARIOL system. Spiking experiments using the NSCLC H446, H1299, HCC827 and SKMES cell lines in normal blood were used to evaluate the detection method.

Results: Twenty five and 12 of 30 patients’ samples were evaluable for analysis at baseline and after the 3rd cycle, respectively. CTCs could be detected in 56% (14/25) and 85.7% (10/12) patients at baseline and after the 3rd cycle of chemotherapy.
respectively. Giemsa staining revealed tumor cells in 60% (15/25) at baseline and in 67% (8/12) after 3rd cycle. PD-1 expression was observed in 71.4% (10/14) and 10% (1/10) (p = 0.044) of the CTC-positive patients at baseline and after the 3rd cycle, respectively. Conversely, PD-L1 was observed in 42.9% (6/14) and 50% (5/10) (p = 0.311) of the CTC-positive patients at baseline and after the 3rd cycle. Among the total number of detected CTCs, 47.8% were PD-1-positive at baseline and 30% after the 3rd cycle whereas, 35.7% and 50% at baseline and after the 3rd cycle, respectively, were PD-L1-positive.

Conclusions: PD-1- and PD-L1 positive CTCs can be observed during the treatment of metastatic NSCLC, suggesting that they can be used as a potential biomarker to monitor the expression of PD-L1 on tumor cells during the clinical phases of the disease and understand the mechanisms of tumor immune escape.

Legal entity responsible for the study: N/A
Funding: Laboratory of Translational Oncology, School of Medicine, University of Crete
Disclosure: All authors have declared no conflicts of interest.

Methods: Peripheral blood was collected from 124 pts with diverse staging and histology at three clinical sites prior to diagnostic biopsy, with some having follow-up draws. All nucleated cells were plated onto glass slides and circulating cells of interest identified by immunofluorescence and morphological features. Prognostic capacity of PD-L1(+) cells (CK +/−, CD45−, malignant nuclear morphology) were assessed with Kaplan-Meier and Cox Proportional Hazard (PH) models.

Results: When detected, PD-L1 subcellular localization was primarily membranous. Pts with >1 PD-L1(+) cell/mL in baseline samples had worse overall survival (OS) (n = 22/124, mOS: 17.2 months vs. not reached, HR = 3.22, p = 0.0051) and follow-up (n = 5/22 mOS = 2.1 months vs. not reached, HR = 4.25, p = 0.0302). High baseline PD-L1(+) cell burden was additive and independent to AJCC staging in Cox PH models (HR = 2.32, p = 0.0447). Single-cell sequencing is underway.

Conclusions: In a multicenter cohort, circulating PD-L1(+) and CD45(−) cell burden predicted worse OS in pre-biopsy and follow up lung cancer blood samples. This warrants prospective investigation as a predictive biomarker to PD-1 axis immune checkpoint inhibitors.

Clinical trial identification: HHSIS261201200049C
Legal entity responsible for the study: National Cancer Institute, EpiSciences
Funding: National Cancer Institute, EpiSciences
Disclosure: R. Graf, D. Lu, R. Krupa, J. Louw, L. Dugan, A. Jendrisak, S. Orr, K. Bethel, Y. Wang, M. Landers, R. Dittamore: EpiSciences Employee. All other authors have declared no conflicts of interest.
Tumor mutation load assessed by FoundationOne (FM1) is associated with improved efficacy of atezolizumab (atezo) in patients with advanced NSCLC

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Background: In patients (pts) with NSCLC, the efficacy of atezo (anti-PD-L1) correlates with PD-L1 expression on tumor cells (TC) and tumor-infiltrating immune cells (IC). We further examined the association between tumor mutation load (ML) and efficacy of atezo in pts with NSCLC.

Methods: We selected 254 2L+ NSCLC pts treated on three Phase 2 trials of atezo mono-therapy (POPLAR, a trial comparing atezo vs docetaxel; doc; BIRCH and F1R, single-arm studies in PD-L1–selected pts) were available for targeted genetic sequencing using the Foundation Medicine (FM) panel of 155 cancer-related genes. ML was quantified for each sample and efficacy was assessed in groups defined by 75th (high), 50th (median) and 25th (low) percentile of the study-specific ML. TIL infiltration was assessed by H&E staining. T efficiency was assessed with ChIP. Atezo efficacy was examined at the following data cutoffs: POPLAR, May 8, 2015; BIRCH, May 25, 2015; F1R, Jan 7, 2015. Results: Across all samples, the median ML was 9.9 MB (range 0.44–411, 25%–75% percentile 5.1–16.6). OS, PFS and ORR were improved in pts with increased ML treated with atezo in both unselected pts (POPLAR) and PD-L1–selected pts (BIRCH; F1R; see Table). ML predicted to atezo efficacy independently of PD-L1 status. ML was not associated with efficacy in pts treated with doc in POPLAR. Associations of ML with PD-L1 expression on TC and IC, TIL infiltration and T efficiency gene expression will be presented.

Conclusions: We demonstrated for the first time that increased tumor ML assessed by the FM1 targeted sequencing panel is associated with improved outcomes with atezo in 2L+ NSCLC. The association between ML and atezo efficacy was seen in both unselected and PD-L1–selected NSCLC pts. ML did not appear to be prognostic in pts treated with doc. Therefore, in addition to PD-L1, ML by FM1 may be an independent predictor of improved responsiveness to atezo in 2L+ NSCLC.

<table>
<thead>
<tr>
<th>ML cutoff</th>
<th>BEP a = 0.87</th>
<th>Low median 96</th>
<th>Med 44</th>
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<tr>
<td>OS (unselected)</td>
<td>HRb 0.80 (0.51, 1.26) 0.53 (0.22, 1.27) 0.32 (0.18, 0.55)</td>
<td>0.88 (0.55, 1.42) 0.49 (0.25, 0.97) 0.33 (0.12, 0.98)</td>
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<tr>
<td>PFS (unselected)</td>
<td>HRb 0.75 (0.52, 1.10) 0.64 (0.37, 1.11) 0.39 (0.22, 0.71)</td>
<td>0.51 (0.35, 0.74) 0.29 (0.17, 0.49) 0.17 (0.10, 0.30)</td>
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<tr>
<td>ORR (unselected)</td>
<td>HRb 0.49 (0.30, 0.81) 0.37 (0.19, 0.72) 0.22 (0.11, 0.47)</td>
<td>0.51 (0.35, 0.74) 0.29 (0.17, 0.49) 0.17 (0.10, 0.30)</td>
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</tbody>
</table>

PD-L1 expression assessment in Non-Small-Cell Lung Cancer shows stability on Ventana’s XT Benchmark platform – “Harmonization study”

T. Neuman1, G. Vainer2

1Pathology, Hadassah Ein Kerem, Jerusalem, Israel, 2Pathology, Tel Aviv Sourasky Medical Center (Ichilov), Tel Aviv, Israel

Background: Pembrolizumab is a monoclonal antibody against programmed cell death 1 (CD279; PD-1), recently approved by the FDA as a 2nd line therapy in NSCLC with a companion diagnostic (PD-L1 22C3; Dako). Today, the only validated IHC platform for PD-L1 detection is the Link-48 platform (Dako), which lowers the availability of the test. Ventana’s benchmark XT platform is a widespread IHC platform. However, data about its reliability and reproducibility using the 22C3 antibody is lacking.

Methods: A comprehensive calibration of the 22C3 PD-L1 staining on the Benchmark XT platform (Ventana) was performed by combining the FDA-approved, pre-diluted 22C3 anti-PD-L1 primary antibody (Dako) with two of Ventana’s DAB detection systems, UltraView and OptiView. After receiving a comparable IHC pattern, 41 NSCLC random cases were independently evaluated by 2 expert pathologists for PD-L1 protein expression, using both platforms, defining the tumor proportion score (TPS): the percentage of tumor cells showing complete or partial membrane staining. Each case was classified as PD-L1 negative, weakly positive, or strongly positive (<1%, 1–49%, and ≥50% PD-L1 TPS, respectively). The scores obtained have been compared, Pearson’s correlation score was calculated.

Results: Using the Dako IHC platform 8, 7 and 26 cases were stratified as PD-L1 strongly positive, weakly positive and negative cases, respectively. Using the Ventana’s UltraView protocol 36/41 cases (87.8%) had the same results, including the 8 strongly positive cases. Pearson’s correlation score indicate a high concordance (0.91; p value <0.0001). Using the Ventana’s OptiView protocol 35/41 cases (85.3%) had the same results, including the 8 strongly positive cases. Pearson’s correlation score indicate a high concordance (0.89; p value <0.0001). Furthermore, the intra-observer correlation of both pathologists was even higher (0.94; p value <0.0001).

Conclusions: Pembrolizumab treatment for NSCLC patients is coupled to the PD-L1 TPS by Dako. The Ventana’s benchmark XT platform can also be used safely to stratify patients with the same algorithm. We provide a defined PD-L1 IHC protocol which is easy to replicate as we used commercially available pre-made reagents only.

Legal entity responsible for the study: Hadassah Medical Center, Jerusalem, Israel. Tel Aviv Medical Center, Tel Aviv, Israel.

Funding: MSD

Disclosure: G. Vainer: Received advisory or consultant fees from Roche, Pfizer, AstraZeneca and MSD. All other authors have declared no conflicts of interest.
mutation in the splice site 1941 + 1G > A for the transcriptional adaptor zinc finger 2. Additional mutations are described in the Table below.

### Table: 7BP

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<td>CDKN2A/B</td>
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<td>S12*</td>
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<td>CREBBP</td>
<td>R1443fs*10</td>
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<tr>
<td>EGFR</td>
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<tr>
<td>NCOA1</td>
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<td>NOTCH3</td>
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<td>RELA</td>
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### Conclusions:
- Present genomic analyses revealed CREBBP alterations in extreme responders to PD1 inhibition independently by the tumor type. CREBBP is ubiquitously expressed and it is known to play many different roles in immune response. Functionally, the described mutations could impair histone acetylation and transcriptional regulation of CREBBP targets. This association deserves validation in a wider anti-PD1 treated cohort of pts but it suggests that CREBBP mutations could have a potential role as predictive biomarker for immunological treatments.

### Legal entity responsible for the study:
- START Madrid-CIOCC

### Funding:
- START Madrid-CIOCC

### Disclosure:
- All authors have declared no conflicts of interest.

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### Table: 8BP

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<th>CD8</th>
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<th>Median</th>
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<td>CD4</td>
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<td>30</td>
<td>0-120</td>
<td>16.7</td>
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### Conclusions:
- These results suggest that HIV- positive patients should feature in clinical trials assessing PD1/PD-L1 checkpoint inhibitors, and this score could be a better tool for the selection of patients that may benefit from immunotherapies.

### Legal entity responsible for the study:
- APHP, Tenon University Hospital, Paris, France

### Funding:
- This study received support from "CARDHP AO n°23 autonome 2014" and from "Fonds de dotation 2015 Recherche en Santé Respiratoire AO autonome 2015"

### Disclosure:
- All authors have declared no conflicts of interest.

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### Table: 9BP

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### Conclusions:
- Biomarkers in cancer immunotherapy: analysis of clinical, histological and immunohistochemical factors associated with PD-L1 status

### Background:
- Immunotherapies targeting the programmed cell death protein 1 (PD-1) to PD ligand 1 (PD-L1) checkpoint have improved prognosis in non-small cell lung cancer (NSCLC). PD-1/PD-L1 status has not been investigated in human immunodeficiency virus (HIV) - positive patients. This study sought to assess PD-L1 status and tumor immune-cell infiltration in NSCLC in HIV patients.

### Methods:
- Consecutive HIV patients treated for NSCLC between 1996 and 2014 at Tenon hospital (Paris, France) were enrolled. PD-L1 tumor expression was assessed using immunohistochemistry (2 antibodies: 1. Chen, clone 5H1 and Cell Signaling, clone EILIN). Tumor immune cell infiltration was assessed for CD3 (3P), CD4 (14F6), CD8 (CD144b), CD20 (L26), CD163 (10D6) and MPO (59A5). The percentage of PD-L1- and immune-positive cells was ≥5%. The score used is the product of intensity ([0, 1, 2, 3]) by positive cell percentage. The PD-L1 score was considered positive if ≥5%. PD-L1 status and immune-cell infiltration results were compared to those of 54 NSCLC from unknown HIV positive status patients.

### Results:
- In total, 34 HIV-positive patients were evaluated: predominantly men (88.2%) with a median age of 51 years and adenocarcinomas (76.5%) with 38.2% stage IV. The median blood CD4 count was 480/μL (86-1120) and 64% exhibited undetectable viral load. The PD-L1 score was higher in HIV-positive patients (EILIN clone: 0 [0-150] vs. 0 [0-28.7], p = 0.047; 5H1 clone: 0 [0-26.7] vs. 0 [0-26.7] p < 0.001).’’’

### Background:
- Immunochemistry is currently the most explored biomarker, but its predictive value is still unclear.

### Methods:
- Between January 2014 and July 2015, 346 patients were candidate for treatment with anti-PD-1/PD-L1 antibodies (pembrolizumab P, durvalumab D or atezolizumab A) at Gustave Roussy Cancer Campus. We reviewed in detail the files of 309 patients for whom PD-L1 expression could have been measured. Clinical, histological and IHC features were retrospectively collected for all of them in order to identify factors affecting PD-L1 status.

### Results:
- 83 patients (26.9%) were positive for PD-L1 in IHC. PD-L1 positivity varied significantly depending on the treatment considered: P = 32.9; D= 30.5 et A = 11.5% (p = 0.002). This suggests a relation between the companion test used for IHC and PD-L1 positivity. Univariate analysis showed that PD-L1 expression was
associated with IHC test and histological type. In multivariate analysis, IHC test and histological type remained significant (respectively p = 0.001 and 0.008). Atezolizumab companion test (SP142) was associated with low PD-L1 expression, while squamous cell carcinoma and urinous carcinoma were associated with high expression. Among metastatic patients, samples from liver metastasis showed a trend for lower PD-L1 expression. There was no significant relationship with sampling method (biopsy or surgical resection), histological analysis place (private or academic), sample size, age or cellularity; or sample location (primary or metastatic site). There was no difference between samples acquired before or after some anticancer treatment.

Conclusions: This study identified that IHC test and histological type were associated with PD-L1 status, which need to be further investigated. The trend for lower PD-L1 expression in metastatic sample needs to be confirmed and compared with clinical response data.

Legal entity responsible for the study: Gustave Roussy Cancer Campus

Funding: Gustave Roussy Cancer Campus

Disclosure: C. Massard: Honoraria from Genentech, Celgene, MedImmune; J-C. Soria: Consultancy fees from MSD, AstraZeneca, Roche-Genentech. All other authors have declared no conflicts of interest.

Background: Regulatory T-cells (Treg) are highly heterogeneous populations with their TGF-β expression in liver metastasis sample needs to be confirmed and compared with clinical outcome was investigated.

Results: All authors have declared no conflicts of interest.

Funding: National Cancer Institute, National Institutes of Health, USA

Disclosure: C. Herrero-Vicente: Honoraria from National Cancer Institute, National Institutes of Health, USA. All other authors have declared no conflicts of interest.

Background: Recent clinical studies have evaluated TILs in TNBC patients, as well as their correlation with the patients' clinical outcome was investigated.

Methods: Using our BC database with 756 pts, we identified 164 TNBC treated with chemotherapy-naive patients with stage III/IV NSCLC and 31 healthy donors (HD) was analyzed with flow cytometry for the presence of the different Treg subtypes in the peripheral blood (PB) of NSCLC patients, as well as their correlation with the patients' clinical outcome was investigated.

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Serum interleukin-6 as a prognostic biomarker for survival in patients with unresectable pancreatic cancer

I. Chen1, C. Dehliendorf1, B.V. Jensen1, P. Pfeifer2, S.E. Nielsen1, N.H. Holländer3, M.K. Yamazaki1, A. Johansen1
1Oncology, Herlev and Gentofte Hospital, Herlev, Denmark, 2Research Center, Danish Cancer Society Institute of Cancer Biology, Copenhagen, Denmark, 3Department of Oncology, Odense University Hospital, Odense, Denmark, 4Oncology, Zealand University Hospital, Naestved, Denmark, 5Department of Oncology, Aalborg University Hospital, Aalborg, Denmark

Background: Patients with pancreatic cancer (PC) have the highest mortality rate of all major cancers. Interleukin-6 (IL-6) is produced by PC cells and macrophages, regulates inflammation and plays an important role in cachexia. The aim of this biomarker study was to determine the clinical utility of serum IL-6 as a prognostic factor. We further explored age, sex, CA 19.9, PS, stage and chemotherapy type as predictors of outcome in patients receiving palliative chemotherapy.

Methods: 452 patients with unresectable PC (M/F: 317/135; median age 67.5 (IQR 61.8-73.0); ECOG Performance Status (PS) of 0/1/2/3: 179/144/124/35; locally advanced disease/metastatic: 67/385; treated with gemcitabine: 145; 32% associated with high expression of IL-6, 32% with moderate expression of IL-6 and 32% with low expression of IL-6) were included. IL-6 was determined by ELISA and OS was determined by Kaplan-Meier analysis.

Results: Patients were grouped into quartiles according to baseline IL-6 values (0.8 to 3.2, 3.2 to 6.4, 6.4 to 14, and ≥14 pg/ml) and CA 19.9 values (1 to 119, 119 to 992, 992 to 7280, and ≥7280 U/ml). A univariate analysis of IL-6 ≥6 pg/ml vs CA 19.9, PS, stage, chemotherapy type and age showed that IL-6 ≥6 pg/ml was associated with low OS (0.91, 95% CI: 0.91–0.95, P = 0.0001), 0.81 (95% CI: 0.78–0.85, P < 0.001), 0.82 (95% CI: 0.78–0.86, P < 0.001) and 0.82 (95% CI: 0.78–0.86, P < 0.001) for IL-6 ≥6 pg/ml vs PS = 0, 1 and 2 and CA 19.9 ≥7280 U/ml, respectively. Multivariate cox analysis showed that apart from age and sex all variables were independently associated with short OS. The hazard rate of death for patients with IL-6 ≥14 pg/ml was 2.23 times as high as those with IL-6 <3.2 pg/ml (95% CI: 1.65 to 3.01, P < 0.001). An increase in IL-6 at the time of the first CT assessment was also associated with short OS (HR 1.20, 95% CI: 1.04–1.38, P < 0.01).

Conclusions: The level of serum IL-6 is a strong independent prognostic biomarker in patients with unresectable PC that could be used to identify patients with poor outcome. Care predictive for survival.


Legal entity responsible for the study: Inna Chen

Funding: Herlev Hospital

Disclosure: All authors have declared no conflicts of interest.

Biomarker analysis to predict the pathological response of locally advanced gastric cancer to neoadjuvant chemotherapy: an exploratory study of the randomized phase II COMPASS trial

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Background: The COMPASS trial is a randomized, phase II study to compare two and four courses of neoadjuvant chemotherapy (NAC) with S-1/cisplatin (SC) and paclitaxel/cisplatin (PC) in patients with locally advanced gastric cancer. Among the 83 enrolled patients, the pathological response, defined as regression of the primary tumor by more than one third, was 46% for SC and 26% for PC. The ability to predict the pathological response would greatly facilitate the selection of patients most likely to benefit from NAC as well as those in whom NAC should be continued. We conducted a biomarker study as part of the COMPASS trial to identify predictors of the pathological response to NAC.

Methods: We collected endoscopic biopsy specimens of the primary tumor before NAC. After ligation of mRNA from the paraffin-embedded specimens, the expression levels of 127 genes were quantified by RT-PCR. The relations between gene expression levels and a pathological response of ≥2 grade 1b were investigated. We studied genes with expression profiles that showed significant interactions with the pathological response to either the SC or PC regimen (P < 0.01).

Results: Among 83 patients enrolled in the COMPASS trial, mRNA extracted from 80 patients (96.4%) was quantifiable. Interaction analyses showed that TIMP1, RRM1, MUC2, DSG2, EGFPR, ZDHHC4, and CLDN18 were significant predictors of the pathological response to NAC with either SC or PC. A marked pathological response to SC was associated with high expression of TIMP1, RRM1, MUC2, and DSG2 and low expression of EGFPR, ZDHHC4, and CLDN18. A marked pathological response to PC was associated with low expression of TIMP1, RRM1, MUC2, and DSG2 and high expression of EGFPR, ZDHHC4, and CLDN18.

Conclusions: The results of an analysis of mRNA in paraffin-embedded endoscopic biopsy specimens obtained from patients with locally advanced gastric cancer could be used to predict the pathological response to neoadjuvant chemotherapy. The expressions of several genes can predict the pathological response to SC and PC.
the association between tumor location and anticancer treatment efficacy in mCRC patients with a RAS/BRAF WT primary tumor.

Methods: Data from three Aman-gsponsored clinical trials were analyzed for treatment outcomes in relation to location of the primary tumor. All studies were randomized: a first-line phase 3 PRIME (NCT01364013), a first-line phase 2 (PEAK, NCT00819780) and a second-phase 3 (181, NCT00339183) study. In order to have a biomarker refined patient population, only RAS/BRAF WT cases were included. Information on tumour location at the time of diagnosis was obtained from the full text descriptions and from the original pathology reports. Primary tumors located in the caecum to transverse colon were coded as right-sided and tumors located from the splenic flexure and from the original pathology reports. Primary tumors located in the caecum to transverse colon were coded as right-sided and tumors located from the splenic flexure and from the original pathology reports. Primary tumors located in the caecum to transverse colon were coded as right-sided and tumors located from the splenic flexure and from the original pathology reports. Primary tumors located in the caecum to transverse colon were coded as right-sided and tumors located from the splenic flexure.

Results: Tumor location ascertainment rate was greater than 80%. Between 80% and 85% of cases are left sided. Results for overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) for each treatment arm in the 3 studies are summarized in table 1. Patients with right-sided tumors did worse for all parameters compared to left sided. Panitumumab provided better outcomes than the comparator on the left side. On the right side, the small number of patients does not allow drawing definitive conclusions, but a lack of efficacy of chemotherapy provide a benefit over chemotherapy with or without bevacizumab in patients with right-sided primary tumors.

Conclusions: The result of these retrospective analyses on a homogenous RAS/BRAF WT subpopulation confirms that primary CRC arising on the right side is associated with poor prognosis regardless of treatment received. Moreover, panitumumab plus chemotherapy provide a benefit over chemotherapy with or without bevacizumab in patients with right-sided primary tumors.

Legal entity responsible for the study: Aman Ltd

Funding: Aman Ltd


The prognostic impact of RAS and RAF serum mutations in localized colon cancer

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Background: The prognostic impact of RAS/RAF mutations in localized colon cancer needs clarification. Based on analysis of tumour specific DNA this study aimed at elucidating the prognostic impact of mutational status in serum using an expanded panel of mutations.

Methods: Stage I-III curatively resected colon adenocarcinoma patients (n = 294) were retrospectively included. Mutations and mismatch repair (MMR) status in tumor were determined at time of operation. The status (categorical) of mutated ctDNA in preoperative serum samples was obtained for patients with tissue mutations. Analyses were performed with droplet digital PCR technology. Hazard ratio (HR) for the association between mutation status and survival was estimated in multivariate analysis taking known prognostic factors into account. Primary endpoints were overall survival (OS) and disease free survival (DFS) and median follow-up was 3.9 and 3.0 years, respectively.

Results: Mutational status in tumor alone (n = 189) had no prognostic impact (p = 0.22). Patients with RAS mutated DNA in both tumor and serum (n = 36) had a significantly worse prognosis, OS (HR= 3.45, 95%CI 1.52-7.85, p = 0.0032) and DFS (HR= 3.61, 95%CI 1.70-7.67, p = 0.0008). Mutational load had significant prognostic impact as well.

Conclusions: Mutational status in tumor did not demonstrate any prognostic impact. RAS mutations in serum, and RAF mutation in serum combined with MMR in tumor were both strong independent prognostic factors.
Impact of Kras mutant subtypes on PD-L1 expression in lung adenocarcinoma

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Background: Clinical responses to immune checkpoint blockade by anti-PD-1/PD-L1 antibodies are associated with antitumor adaptive immune responses. PD-L1 is expressed in 37% of Kras mutant LUAD, suggesting PD-L1 as a potential target for anti-PD-1/PD-L1 therapy. However, it remains unclear whether differences among Kras mutant subtypes can affect PD-L1 expression.

Methods: PD-L1 expression by tumor cells induced by Kras mutations led to decreased PBMCs proliferation compared to Kras wild type (WT) vs. mutant type (MT) were following, RR 66.6% vs. 16.7%, DCR, 87.5% vs. 66.7%, respectively (CR 20%, PR 45%, SD 13.3%, PD 9/2). The median PFS and OS in Kras WT vs. MT were as follows, 8.9 months (ms) vs. 5.6 and 20.8 ms vs. 10.3 ms, respectively. KRAS MT showed extremely shorter PFS and OS compared with KRAS WT (P = 0.0008 and 0.0008).

Results: Our data suggested HER2-positive AGC harbored KRAS mutation at the low frequency. KRAS mutation might predict poor prognosis as receiving HER2 targeted treatment. Further investigation was warranted to confirm the predictive value of KRAS status in HER2-positive AGC treated with trastuzumab to fluoropyrimidine plus CDDP. We will present additional analysis of KRAS amplification in this cohort at the convention.

Legal entity responsible for the study: N/A

Funding: Japanese Foundation for Cancer Research

Disclosure: All authors have declared no conflicts of interest.

An extended KRAS mutation test for the detection of 28 common mutations in FFPE and plasma specimens

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Background: The KRAS oncogene is frequently mutated in human cancers. In addition to KRAS codons 12, 13, 61 hotspot mutations, recent clinical trial data revealed that mutations in KRAS codons 59, 116 also predict poor response to anti-epidermal growth factor receptor (EGFR) therapy in patients with metastatic colorectal cancer (mCRC). Detection of an extended set of KRAS mutations in colorectal cancers tissues is now accepted clinical practice.

Methods: The KRAS Mutation Test v2 (Life Science Research, LSR) is a real-time PCR assay, which detects 28 mutations in codons 12, 13, 59, 61, 116 and 146 of the KRAS gene in DNA derived from formalin-fixed, paraffin-embedded tissue (FFPE) as well as plasma specimens. Mutations are detected by allele-specific amplification in three multiplex PCR reactions on the cobas 4800 analyzer. LOD studies were performed using contrived tissue and plasma samples. For method correlation, 301 FFPE specimens and 636 plasma specimens were tested with the KRAS Mutation Test v2 (LSR) and MiSeq (Illumina) sequencing as the reference method.

Results: Using preliminary analysis parameters, the KRAS test has shown it can detect at least 1% mutant sequence in a background of wild-type DNA for tissue, and at least 100 mutant sequence copies per mL for plasma in the LOD studies. Preliminary method correlation results revealed >98% overall concordance for tumor FFPE and >99% overall concordance for cell-free DNA samples with MiSeq reference data. Final results will be presented.

Conclusions: The KRAS Mutation Test v2 (LSR) demonstrated strong initial analytical performance for the detection of 28 KRAS mutations. It is a sensitive, robust and reliable assay with a quick turnaround time which can be used on both tissue and liquid biopsies.

Legal entity responsible for the study: Roche Molecular Systems

Funding: Roche Molecular Systems

Disclosure: All authors have declared no conflicts of interest.

Plasma YKL-40 as a biomarker for poor prognosis in patients with metastatic colorectal cancer treated with 3-line cetuximab and irinotecan

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Background: Trastuzumab targeted on HER2 has been shown to confer overall survival benefit adding to fluoropyrimidine (Fp) plus CDDP in HER2-positive advanced gastric cancer (AGC). HER2 is known to make the formation of heterodimer with EGFR. Therefore HER2 and EGFR heterodimer is a common downstream of HER family signaling pathway.

Methods: Of 100 patients received Fp plus CDDP with trastuzumab as 1-line between March 2011 and November 2015, total 77 patients with sufficient specimen for DNA extraction were enrolled in this analysis. Multiple gene expression of HER family common downstream was performed on archival samples using Lumines Assay (MERGEN and GENOSEARCH Mul-PACK, MBL) for KRAS and NRAS including exon 2, 3 and 4, PIK3CA and BRAF. Tumor response was re-assessed by the investigator retrospectively by RECIST1.1.

Results: KRAS mutation of exon2 was detected in only 6 patients of 77 patients (7.8 %). No mutations were found in NRAS, PIK3CA and BRAF in this HER2 positive AGC series. Overall RR and disease control rate (DCR) in KRAS wild type (WT) vs. mutant type (MT) were following, RR 66.6% vs. 16.7%, DCR 87.5% vs. 66.7%, respectively (CR 20%, PR 45%, SD 13.3%, PD 9/2). The median PFS and OS in Kras WT vs. MT were as followed, 8.9 months (ms) vs. 5.6 and 20.8 ms vs. 10.3 ms, respectively. KRAS MT showed extremely shorter PFS and OS compared with KRAS WT (P = 0.0008 and 0.0008).

Conclusions: Our data suggested HER2-positive AGC harbored KRAS mutation at the low frequency. KRAS mutation might predict poor prognosis as receiving HER2 targeted treatment. Further investigation was warranted to confirm the predictive value of KRAS status in HER2-positive AGC treated with trastuzumab to fluoropyrimidine plus CDDP. We will present additional analysis of KRAS amplification in this cohort at the convention.

Legal entity responsible for the study: N/A

Funding: Several Foundation for Cancer Research

Disclosure: All authors have declared no conflicts of interest.

KRAS status and HER2 targeted treatment in advanced gastric cancer


Background: Trastuzumab targeted on HER2 has been shown to confer overall survival benefit adding to fluoropyrimidine (Fp) plus CDDP in HER2-positive advanced gastric cancer (AGC). HER2 is known to make the formation of heterodimer with EGFR. Therefore HER2 and EGFR heterodimer is a common downstream of HER family signaling pathway.
Chitinase activity can predict liver metastases in colorectal cancer in blood

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Background: DNA damage accumulation and telomere dysfunction is associated with the development of cancer. However, we do not know the exact role of DNA damage and telomere dysfunction in metastases of colorectal cancer. We have previously identified biomarkers for DNA damage and telomere dysfunction. In this study we evaluated the role of chitinase activity (one of the biomarkers) in blood in predicting liver metastases of colorectal cancer.

Methods: The levels of chitinase activity were examined in 401 colorectal cancer patients, including 53 synchronous liver metastases in peripheral blood. 347 colorectal cancer patients' peripheral blood activities were measured before resection of the cancer. The clinical parameters were collected, and the patients were prospectively followed up.

Results: The average age of the cancer patient was 65 years old, the chitinase activity was significantly over-expressed in synchronous liver metastases when compared with colorectal cancer patients who had no metastases. During the follow up in 347 colorectal cancer patients, higher expression of chitinase activity, higher risk of liver metastases, both univariate Cox analysis (HR 2.54, 95% CI 1.17-5.51) and multivariate Cox analysis (HR 5.3) showed chitinase has high predictive value for liver metastases after resection of the primary colorectal cancer. Kaplan-Meier analysis shows the chitinase activity has significant correlation to survival in colorectal cancer patients. The metastasis ratio between two groups in non-synchronous colorectal metastasis patients.

Conclusions: Taken together, the findings in this study provide experimental evidence that chitinase activity is a potentially predictive biomarker for liver metastases in colorectal cancer.

Legal entity responsible for the study: N/A

Funding: National Natural Science Foundation of China (NSFC)

Disclosure: All authors have declared no conflicts of interest.

Table: 7TP

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<th>Three years</th>
<th>Five years</th>
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<td>9.5% (20/211)</td>
<td>10.4% (22/211)</td>
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<tr>
<td>High chitinase activity</td>
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<td>16.5% (19/115)</td>
<td>22.6% (26/115)</td>
</tr>
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*Cut-off value = 22.8026


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Clinical characteristics in colorectal cancer harboring BRAF V600E and non-V600E mutations

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Background: BRAF V600E mutation (MT) in metastatic colorectal cancer (CRC) has been known thoroughly as a prognostic biomarker, and as a negative predictive biomarker for anti-EGFR treatment. On the other hand, the feature of BRAF MTs other than BRAF V600E still remains unclear. This study aimed to reveal the clinical characteristics of BRAF non-V600E MTs compared with the EGFR signaling pathway MTs status including BRAF V600E MT. Methods: Consecutive patients from June 2012 to November 2013 were enrolled in this study. Multiple genotyping of EGFR signaling pathway was performed on archival samples using Luminex Assay (MABGEN, GENOSEARCH Mu-PACK and GENOSEARCH BRAF, MBR) for BRAF V600E / BRAF non-V600E, KRAS including exon 2, 3 and 4, NRAS and PIK3CA. We analyzed the correlation among MTs profile, clinical data and location of CRC. Results: A total of 824 CRC patients was analyzed, consisted of 374 females and 450 males, 147/200, 263 and 214 in stage I, II, III and IV or recurrent CRC, respectively. The incidence of MTs were as followings, BRAF V600E / BRAF non-V600E, KRAS including exon 2, 3 and 4, NRAS and PIK3CA were 5.3% / 1.7%, 41.5%, 3.3% and 9.7%, respectively. The relationship among main characteristics and mutational status showed in table below. Although RAS and BRAF non-V600E MTs were in a mutually exclusive manner, one case of co-mutation with KRAS A146T MT was observed in BRAF V600E cases. In both BRAF V600E MT and BRAF non-V600E MT, four cases were having co-mutation with PIK3CA MT. Conclusion: In this analysis BRAF non-V600E MTs were identified as a rare fraction and had no specific character revealed in contrast to the BRAF V600E MT, which was more frequent in right-sided primary, female and poorly differentiated histology. Further more large-scale investigation in this rare fraction of BRAF non-V600E MTs will be necessary to clarify its clinical meaning for precision medicine.

Legal entity responsible for the study: N/A
Funding: Japanese Foundation for Cancer Research
Disclosure: All authors have declared no conflicts of interest.

5-fluorouracil degradation rate as a predictive toxicity biomarker in early stage gastrointestinal cancer

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Background: Prediction and early management of severe toxicity might avoid both therapy’s interruption and the benefit loss of adjuvant chemotherapy. However, predictive toxicity biomarkers are not yet available. The aim of this study was to investigate whether polymorphisms of different genes involved in fluoropyrimidine metabolism and 5-fluorouracil (5-FU) degradation rate were associated with clinical outcome of oral fluoropyrimidine-based adjuvant chemotherapy in patients with early stage GI cancer.

Methods: Genotyping of DPYD IVS14 IVS 14 + 1 G > A, MTHFR C677T and A1298C SNPs were performed by pyro-sequencing technology. PCR analysis was used for genotyping TYMS-TSER. Using PBMC cells, we also evaluated the 5-FU degradation rate, which determines the amount of drug consumed by cells in a unit time. Patients were categorized in two groups according to their value of 5-FU degradation rate: below the 5th centile (poor metabolism - PM) or above the 95th centile (ultra-rapid metabolism - UM) and within 5-95th centile (0.85-2.2 ng/ml/106 cells/min).

Results: One hundred forty-two patients with early stage colon (39%), rectal (28%), stomach (20%) and pancreatic (13%) cancer, treated with 5FU-based adjuvant monochemootherapy, were included in this retrospective analysis. Forty-three per cent of patients had a lymphnode-positive disease, and 37% received concomitant radiotherapy. Most of patients had an ECOG PS = 0-1. Seventy-four and 20% of the patients suffered from at least one GI-1 and GI-3 adverse events (12 hematologics, 24 GI, 12 HES), respectively. Sixteen (11%) patients resulted abnormal 5-FU metabolizers. At a multivariate logistic regression analysis, an altered 5-FU degradation rate (<0.86>2.10) resulted significantly associated with both GI-1 hematologic (OR = 2.99, 95% CI 0.98-9.12, P = 0.05) and all grade 3-4 adverse events (OR = 4.39, 95% CI 4.0-10.380, P = 0.01). No correlation was reported between toxicity and each tested gene polymorphism.

Conclusions: Our study showed a statistically significant association between 5-FU degradation rate and both GI-1 hematologic and all 3-4 toxicities. Therefore, the 5-FU degradation rate may be considered as a putative, predictive biomarker of fluoropyrimidine-related toxicity.

Legal entity responsible for the study: N/A
Funding: Self-funded
Disclosure: All authors have declared no conflicts of interest.

Large scale DFNA5 methylation and expression analysis in primary breast adenocarcinoma using data from the Cancer Genome Atlas

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Background: Methylation of promoter CpG islands is frequently associated with transcriptional silencing and may serve as a mechanism to inactivate tumor suppressor genes. Thus, it may play a role in tumor development and progression. Several studies have shown that estrogen receptor- (ER)-positive breast cancer tumors present with higher levels of promoter methylation at several loci compared to ER-negative tumors. However, large-scale analyses in breast cancer have not been conducted.

Methods: We conducted a large scale methylation and expression analysis in primary breast adenocarcinoma using data from the Cancer Genome Atlas (TCGA) including 1,037 breast adenocarcinomas. Genomic DNA was extracted from archival formalin-fixed, paraffin-embedded (FFPE) tumors. Methylation of DNA was assessed by pyrosequencing on the PyroMark Q24 instrument (Qiagen). Bi- and univariate analyses were performed using R software. The results were corrected for multiple testing using Bonferroni and false discovery rate (FDR) methods.

Results: We found that promoter methylation at 21 loci was significantly higher in ER-positive compared to ER-negative tumors. Expression analysis showed that these loci were differentially expressed in breast cancer samples suggesting a functional role of promoter methylation.

Conclusions: Our study provides evidence that promoter methylation is significantly associated with ER-status in breast cancer tumors. These results highlight the importance of applying large-scale methylation and expression analysis in breast cancer to identify potential therapeutic targets and biomarkers.

Legal entity responsible for the study: N/A
Funding: The Fondation Belval for Oncology
Disclosure: All authors have declared no conflicts of interest.

Predictive value of vascular endothelial growth factor A (VEGF-A) for bevacizumab-based treatments across advanced cancers: a meta-analysis based on eight phase III randomized control trials involving 4,623 patients

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Background: Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has been shown to be beneficial for patients with advanced cancer in phase III randomized control trials which had associated biomarker analyses. We aim to evaluate the predictive value of circulating VEGF-A on patient survival in these studies.

Methods: PubMed was searched for eligible trials from the date of inception to 31 December, 2015. Based on the median circulating level of VEGF-A in each trial, we conducted a meta-analysis with random-effect model to estimate the treatment effects between bevacizumab-based treatments and treatments without bevacizumab on progression-free survival (PFS) and overall survival (OS). Interaction test was used to examine the predictive value.

Results: Eight studies were included, involving 4,623 patients analyzed with VEGF-A level. Patients following bevacizumab-based treatments had significantly prolonged PFS regardless of VEGF-A level (high: HR = 0.70 [95% CI 0.63-0.77], P = 0.001, I2=12%; low: HR = 0.87 [0.79-0.87], P < 0.001, I2= 3%). No significant interaction effect was observed (Chi2 = 3.15, P = 0.12). Although significant benefit on OS was exclusively shown in patients with higher VEGF-A level (high: HR = 0.83 [0.73-0.95], P = 0.005, I2= 0%; low: HR = 0.96 [0.83-1.0], P = 0.05, I2= 4% but there was still no interaction effect between stratified groups (Chi2 = 2.5, P = 0.14). Subgroup analysis revealed potential VEGF-A subgroup differences in patients with breast cancer and gastric cancer but not lung cancer and colorectal cancer. However, tumor type was not a source of heterogeneity during synthesis on PFS or OS.

Conclusions: There is still insufficient evidence to support the use of VEGF-A as a predictive biomarker for bevacizumab-based treatment in advanced cancers.

Legal entity responsible for the study: N/A
Funding: The First Affiliated Hospital of Guangzhou Medical University
Disclosure: All authors have declared no conflicts of interest.
genes in breast cancer. We hypothesize that DFNA5 promoter methylation may be a valuable epigenetic biomarker, based on strong indications for its role as tumor suppressor gene, its function in programmed cell death and its potential role as biomarker in cancer.

Methods: In this study we analyzed DFNA5 methylation in a high number of samples using publicly available data from TCGA. Infinium HumanMethylation450k data, covering 22 different CpGs in the DFNA5 gene, from 668 female breast adenocarcinoma samples and 79 paired normal breast samples. We observed a significant conversion rate in Ki-67, estrogen receptor (ER), progesterone receptor (PR) and HER2 between primary breast cancer and relapse and their value as a prognostic factor.

Results: A significant difference in DFNA5 methylation (N = 79) between primary tumor and paired normal breast samples was found for all 22 CpGs (p < 0.001). A significant higher DFNA5 methylation was found in lobular compared to ductal adenocarcinoma in 11 out of 22 CpGs (p < 0.05). The same is true for DFNA5 expression (p < 0.01). A physical map was constructed to correlate the chromosomal location of the 22 CpGs with the average methylation values of the different subgroups (normal vs. tumor). A clear clustering of the methylation values at the different positions was observed. The methylation values of the first 6 CpGs, located in the gene body, were always higher in the normal samples compared to the tumor samples. In contrast, for CpG7 till CpG20, located in the gene promoter region, the average methylation values were similar in the two groups. For the remaining 15 CpGs, the methylation values were again higher in normal samples. Finally, we showed that ER state is associated with DFNA5 methylation in 18 CpGs (p < 0.05). A clear clustering of the methylation values at the different positions was observed. The methylation values of the first 6 CpGs, located in the gene body, were always higher in the normal samples compared to the tumor samples. In contrast, for CpG7 till CpG20, located in the gene promoter region, the average methylation values were similar in the two groups. For the remaining 15 CpGs, the methylation values were again higher in normal samples. Finally, we showed that ER state is associated with DFNA5 methylation in 18 CpGs (p < 0.05).

Conclusions: These preliminary data suggest a promising role of DFNA5 in breast cancer. In addition, this analysis shows the power of initiatives such as TCGA, providing data for large sample numbers, for the analysis of individual genes involved in cancer.

Legal entity responsible for the study: University of Antwerp

Funding: IWO, University of Antwerp

Disclosure: All authors have declared no conflicts of interest.

T006P Evaluation of the association of HER family members with efficacy of trastuzumab therapy in metastatic breast cancer

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Background: In the current study, we performed a complete analysis of gene amplification, copy number variations (CNV), transcriptional profiling and protein expression of all four HER family receptors, in a series of patients with metastatic breast cancer (MBC), treated with trastuzumab-based regimens. In addition, our analysis included the evaluation of several other factors, such as PTEN and mTOR protein expression by immunohistochemistry (IHC) and PIK3CA mutations.

Methods: Formalin-fixed paraffin-embedded tumor tissue samples were collected from 229 patients, considered to be HER2-positive when assessed at the local laboratories. Central review of HER2 status by fluorescence in situ hybridization and/or IHC revealed that the 229 patients, only 139 (61%) were truly HER2-positive.

Results: In the multivariate analysis, HER2 gene amplification (using the 75th percentile as a cut-off point) (HR = 0.50, 95% CI 0.27-0.93, p = 0.027), HER2 mRNA expression (75th percentile as a cut-off point) (HR = 0.47, 95% CI 0.23-0.97, p = 0.024) and PTEN protein expression (HR = 0.53, 95% CI 0.27-1.02, p = 0.059) were significant independent favorable prognostic factors for TTP in the HER2-positive patients (HR = 0.53, 95% CI 0.27-1.02, p = 0.059). In addition, EGFR CNVs (HR = 4.89, 95% CI 1.23-19.36, p = 0.024), HER2 gene amplification (using the median value as a cut-off point) (HR = 0.41, 95% CI 0.16-1.06, p = 0.067), HER2 protein expression (HR = 0.15, 95% CI 0.04-0.52, p = 0.003) and mTOR protein expression (HR = 0.33, 95% CI 0.13-0.84, p = 0.02) independently affected TTP in the HER2-negative subgroup.

Conclusions: The present study suggests that EGFR is a negative, whereas HER2 is a positive prognostic factor in patients with MBC. Since the above associations were not restricted to HER2-positive patients only, a definitive predictive value for trastuzumab treatment is not documented. Given the retrospective nature of the current analysis, our findings should be considered as hypothesis generating.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group

Funding: Roche Hellas S.A

Disclosure: G. Fountzila: Advisory Board. Roche Hellas S.A. All other authors have declared no conflicts of interest.

T007P Pathology of BRCA1- and BRCA2-associated breast cancers: known and less known connections

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Background: BRCA1 and BRCA2 mutation carriers face an elevated lifetime risk for breast and ovarian cancer diagnosis. BRCA-related tumors display characteristic pathological features, with the BRCA1-associated being predominantly triple-negative. On the contrary, BRCA2-associated tumors are more commonly found to be estrogen/progesterone receptor (ER/PgR)-positive. The incidence of BRCA1 and BRCA2 deleterious mutations in HER2-positive breast cancers, as well as the incidence of BRCA2 deleterious mutations in triple-negative breast cancer cases has not been investigated in depth. Our aim was to explore the clinicopathological characteristics of breast cancers in BRCA mutation carriers in a Greek population.

Methods: Patients diagnosed with breast cancer between 1999 and 2016 were tested for BRCA1 and BRCA2 mutations, either by Sanger sequencing or by next generation sequencing using the Trustus Cancer 94-gene panel. A retrospective review of the medical records was conducted to retrieve patient demographics and tumor histopathological characteristics.

Results: Out of 2096 high-risk breast cancer families tested, we identified 303 BRCA1 and 88 BRCA2 carriers (18.7%). Mean age of breast cancer diagnosis for BRCA1 and BRCA2 carriers was 40.7 years (range 19-74) and 42.8 years (range 25-71), respectively. Information on clinicopathological characteristics (including ER/PgR and HER2 status) was available for 282 (72%) of the 391 mutation carrier patients. Tumor histological subtypes in BRCA1 carriers were predominantly ductal (79%) and medullary (10%), while in BRCA2 carriers these were more frequently ductal (74%) and lobular (15%). Interestingly, 20% of the BRCA2 tumors were triple-negative, in contrast to the expected, significantly higher proportion (75%) observed in BRCA1 carriers (chi-square, p < 0.001). Moreover, a significantly higher percentage of BRCA2 tumors were HER2-positive compared to BRCA1 tumors (24% vs 4.7%, p < 0.001).

Conclusions: These data confirm established observations in the pathology of BRCA-related tumors, but provide further insight on the association of rare pathological and immunohistochemical entities with loss-of-function mutations in these genes, which can be clinically important.

References
Methods: Data on the clinical behavior, RAD50 gene expression (RNA-Seq (V2)) and molecular subtype of tumors.

Results: The methylation of an eight-gene-panel in peripheral blood cells was significantly correlated with BC, and showed outstanding discriminatory power for distinguishing BC cases from non-cancer controls (first validation round with 270 fanatical BC case and 251 non-cancer controls: AUC = 0.94; 95% CI: 0.92-0.96; second validation round with 189 sporadic BC case and 189 non-cancer controls: AUC = 0.93; 95% CI: 0.90-0.96). In addition, these blood-based DNA methylation signatures were similar among BC patients with differential clinical characteristics regardless of stage, receptor status and menopause status. The expression of four genes were also analysed in the leucocytes from 72 subjects and showed inversely correlation with the methylation levels (p < 0.05).

Conclusions: This study reveals a strong association between decreased methylation of genes in peripheral blood and BC, and provides a promising blood-based marker panel for the detection of early BC.

Legal entity responsible for the study: University Hospital of Heidelberg

Funding: This work was supported by the Dietmar-Hopp Foundation, University Hospital of Heidelberg, Helmholtz Society and the German Cancer Research Center (DKFZ). The familial BC samples were collected within a project funded by the Deutsche Krebshilfe (Grant number: 107054).

Disclosure: R. Yang, B. Burwinkel: Inventors of a provisional patent application relating to the subject matter of this manuscript and therefore declare a potential conflict of interests.

107P Evaluation of RAD50 as a prognostic marker of survival in breast cancer patients

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Background: Breast cancer (BC) is common and aggressive malignancy. Resistance to drugs often develops and is not fully understood. One of the possible reasons of this is gene expression fluctuates significantly in breast tumors of various molecular subtypes (except pair of Luminal A and B), between patients on 1st and 2nd stages of disease and patients with different CNA. The patients with high level of RAD50 gene expression had significantly reduced overall survival in comparison with the patients that had low level of RAD50 gene expression only among patients with CNA. Correlation analysis of CNA and level of RAD50 gene expression has shown that high level of RAD50 gene expression bonded with gain and amplification of RAD50 gene.

Conclusions: Our finding allows us to consider the gain and amplification of RAD50 gene as traits which are associated with poor survival of BC patients and RAD50 as a potential prognostic marker of BC.

Legal entity responsible for the study: Knyazova Ramziya Gallyamovna

Funding: Russian Science Foundation (project 15–15–20032)

Disclosure: All authors have declared no conflicts of interest.

108P Identification of breast cancer associated altered DNA methylation in peripheral blood using MALDI-TOF mass spectrometry

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Background: Breast cancer (BC) is the leading cause of cancer-related mortality in women worldwide. Changes in DNA methylation in peripheral blood could be associated with malignancy at early stage. However, the BC-associated DNA methylation signatures in peripheral blood were largely unknown.

Methods: Illumina 27K Methylation Array and Illumina 450K Methylation Array for the discovery of BC-related aberrant methylation sites in peripheral blood. The top hits were selected and validated using the MALDI-TOF Mass Spectrometry (MassARRAY, Agena Bioscience, Inc.) in two independent case-control studies with subjects from different centers. Gene expression levels were measured by real-time PCR and correlated with methylation. The clustering of samples by multiple CpG sites from a total of eight genes was realized by logistic regression. Receiver operating characteristic curve analyses was used to determine the discriminatory power.

Results: The methylation of an eight-gene-panel in peripheral blood cells was significantly correlated with BC, and showed outstanding discriminatory power for distinguishing BC cases from non-cancer controls (first validation round with 270 fanatical BC case and 251 non-cancer controls: AUC = 0.94; 95% CI: 0.92-0.96; second validation round with 189 sporadic BC case and 189 non-cancer controls: AUC = 0.93; 95% CI: 0.90-0.96). In addition, these blood-based DNA methylation signatures were similar among BC patients with differential clinical characteristics regardless of stage, receptor status and menopause status. The expression of four genes were also analysed in the leucocytes from 72 subjects and showed inversely correlation with the methylation levels (p < 0.05).

Conclusions: This study reveals a strong association between decreased methylation of genes in peripheral blood and BC, and provides a promising blood-based marker panel for the detection of early BC.

Legal entity responsible for the study: University Hospital of Heidelberg

Funding: This work was supported by the Dietmar-Hopp Foundation, University Hospital of Heidelberg, Helmholtz Society and the German Cancer Research Center (DKFZ). The familial BC samples were collected within a project funded by the Deutsche Krebshilfe (Grant number: 107054).

Disclosure: R. Yang, B. Burwinkel: Inventors of a provisional patent application relating to the subject matter of this manuscript and therefore declare a potential conflict of interests.

108P HER2 based expression subpopulations in TNBC: pathological aspects and clinical significance

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Background: Triple negative breast cancer (TNBC) is defined as hormone receptors less than 1% and human epithelial growth factor receptor 2 (HER2) negative by immunohistochemistry. HER2 negative tumors can express an intracellular domain and present a HER2 positive phenotype. Before Trastuzumab era, the prognostic was worse in HER2 over expressed early breast cancer than in triple negative counterpart.

Methods: We conducted a retrospective analysis in order to explore the clinical significance of different degrees of tumor HER2 immunohistochemistry expression: 0, 1 or 2 inside triple breast cancer population.

Results: We analysed data from 440 early stage breast cancer patients, primary treated by surgery, addressed to the Department of Medical Oncology of University Hospital of Lille France, for adjuvant chemotherapy, between January 2010 and April 2013. 47 patients (10,6%) had HER2 positive phenotype, 67pts (15,2%) HER2 positive, 32 pts (74,1%) HER2 negative. The mean age of the HER2 positive patients was 47 years, 19 % (4pts) and delirious BRCA1 and BRCA2 mutations were found in 10 pts (21%). The patients were more likely to have stage IIIA 48 % (23pts), invasive ductal carcinoma 74 % (35pts), the surgery was conservative in 28 pts (58pts) and the majority, 46pts (93%) was anthracycline exposed. The distribution of HER2 score among TN patients were as follows: 62% (29pts) negative, 27,6 % (13pts) one plus, 10,4 % (5pts) two plus and negative for in situ hybridization. HER 2 positivity correlated with pT (p = 0, 05), Ki67 (p = 0, 05), and tumor grade (p = 0, 08). Pathologic stage pT, Ki67, and HER2 score were associated with relapse (p < 0, 05). For a median follow up of 38 months (range 24 to 52mo), 8pts (17%) experienced recurrence: loco regional in three cases and distant metastasis in 5pts (10%). The median event free survival (EFS) was 29, 8 months (range 7 to 76 mo) and the median DFS in HER2 + score (29,8mo) respectively in HER2 positive (29,2mo) population than in triple negative HER2 negative (31,8mo), without reaching the significance (P = 0, 9).

Conclusions: The proportion of HER2 positivity inside TNBC population is valuable. The HER2 score 2 correlates with prognostic negative tumor features and associates with poor outcome in our analysis.

Legal entity responsible for the study: University Hospital of Lille France

Funding: University Hospital of Lille France

Disclosure: All authors have declared no conflicts of interest.

108P Genetic influence of EGFR-P38K-mTOR pathway and other loci in triple-negative breast cancer

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Background: Breast cancer (BC) is the most frequent cancer in women. About 15% of all cases account for the most aggressive subtype: triple negative breast cancer (TNBC). TNBC biological heterogeneity has been explained in both gene expression profile studies and genome wide association studies (GWAS). Our study explores the role of single nucleotide polymorphisms (SNP) in TNBC. We hypothesized that new loci can confer risk and prognosis of TNBC, given its well-known tendency to genetic aberrations.

Methods: In this retrospective study, we genotyped a group of SNP in 111 paraffin-embedded tumor samples of patients diagnosed with TNBC (cases) and in 176 blood samples of healthy donors (controls). The SNP were selected from 5 genes (MAP3K1, P38K, TERT, EGFR, and mTOR) known for their implication in TNBC and other types of cancer.

Results: Univariate analysis with chi-square test comparing genotypic frequencies between cases and controls confirmed statistical significance in EGFR rs4947986 (p = 0.001) and TERT rs2731810 (p < 0.001) associated with risk of TNBC development.
These results in EGFR and TERT have not been described elsewhere in the literature. Likewise, our study also indicates the existence of similar associations that influence the risk of developing TNBC in EGFR rs712829 (p = 0.04), MAP3K1 rs1899312 (p = 0.016), PI3K rs2699887 (p = 0.011) and PI3K rs2699905 (p = 0.011). A strong trend towards risk of TNBC was detected (p = 0.050) in mTOR rs2259080.

Our findings not only confirm the genetic influence of molecular pathways in EGFR, PI3K, mTOR and MAP3K1 but also reveal new loci for development of TNBC. Having recognized new TERT and EGFR mutations in our cohort encourages us to keep unveiling plausible new pathways on carcinogenesis and treatment targets for TNBC. However, more translational studies are mandatory.

Legal entity responsible for the study: Hospital Universitar Mutua Terrassa-Oncology and Hematology Department

Funding: Hospital Universitar Mutua Terrassa

Disclosure: All authors have declared no conflicts of interest.

### Abstracts

#### 110P Biomarkers for afatinib and dasatinib treatment in triple negative breast cancer

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Background: Triple negative breast cancer (TNBC) lacks expression of hormone receptors and amplification of HER2. There are currently no approved targeted therapies. EGFR is frequently overexpressed in TNBC and may be a rationally target.

The activity of afatinib, an irreversible pan-HER TKI, was assessed alone and in combination with inhibitors of other promising targets for TNBC.

Methods: Sensitivity to afatinib and other targeted therapies was assessed using receptors and amplification of HER2. There are currently no approved targeted therapies tested. The combination of afatinib with dasatinib showed strong anti-proliferative activity and was further investigated. The afatinib/dasatinib combination was synergistic in 10 of the 14 cell lines. Low levels of Bcl2 were predictive for the combined treatment. Bcl2 cells, which show the strongest synergistic response to the combined treatment, (Y527), was significantly decreased following afatinib/dasatinib treatment. In BT20 cells, which show the strongest synergistic response to the combined treatment, phosphorylation of both ERK1/2 (T202/Y204) and Akt (S473/T308) was significantly reduced following treatment.

Conclusions: Afatinib in combination with dasatinib may have activity in TNBC. Bcl2 may be a predictive biomarker to identify patients who are more likely to benefit from this combination. RPPA results suggest that efficient inhibition of both ERK and Akt signalling may contribute to the synergistic anti-proliferative effects of afatinib combined with dasatinib.

Legal entity responsible for the study: Dublin City University

Funding: Boehringer Ingelheim

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#### 111P The prognostic impact of PI3K/AKT/mTOR pathway aberrations on luminal breast cancer patients

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Background: The exact role of the dysregulation of the PI3K/AKT/mTOR pathway component is not clearly understood. In this study, we aimed to clarify the correlations between each of the pathway components with the presentation and outcome of estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer.

Methods: Immunohistochemistry (IHC) was performed on TMA blocks prepared from samples of 352 luminal breast cancer patients (ER+ /HER2-) who presented for adjuvant treatment to CLB between January 1, 1995 to December 31, 2003. Another validation cohort of 160 patients (from 1999 to 2000) was used to confirm the findings. Patients were followed for a median of 9.2 years (Range: 0.2-13.7 years).

Results: Median age at diagnosis was 58.3 y. Tumors were larger than 2 cm in 36.4% of the cases and 58.5% had axillary LN deposits. Among the whole cohort, 329 patients were assessable for Nuclear LKB1, 331 for cytoplasmic LKB1, 329 for nuclear pAKT, 330 for cytoplasmic pAKT, 335 for p70-s6k(350), 335 for p-e-Akt(319), 319 for p85-pS6k, 339 for p70-p65k and 332 for cytoplasmic IGF1. Nuclear LKB1, cytoplasmic LKB1, nuclear pAKT, cytoplasmic pAKT, p4EBP1, p70-s6k(350), p70-s6k, p85-pS6k and cytoplasmic IGF1 expression was high in 48%, 36%, 55.9%, 19.1%, 43.9%, 22.7%, 71.4%, 27.3 and 55.1% respectively Nuclear pAKT high expression, but not cytoplasmic pAKT expression, was associated with better disease free survival (DFS) (HR = 0.53, 95%CI:0.36-0.79; p = 0.002, OS (HR = 0.48, 95% CI: 0.31-0.75; p = 0.001), smaller tumors (p = 0.002), lower lymph node involvement (p = 0.007) and lower pathological grade. This was confirmed in an independent patient cohort. In contrast, p85-pS6k was associated with poorer DFS (HR = 1.65, 95%CI: 1.08-2.50; p = 0.02) and OS (HR = 1.85; 95%CI: 1.09-3.13; p = 0.022). Neither p-e-Akt nor p70-s6k expression showed any prognostic significance. In the overall cohort, no association between IGF1 and DFS or OS was found.

Conclusions: Higher nuclear pAKT is associated with better prognosis while the downstream markers of mTOR activation as p85-pS6k are associated with poorer prognosis.

Legal entity responsible for the study: Centre Leon Berard

Funding: Centre Leon Berard

Disclosure: All authors have declared no conflicts of interest.

#### 112P 3-biomarker HRD score versus individual biomarker (LOH, TAI, LST) scores in platinum treated serious ovarian cancer (SOOC)

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Background: Previous studies have shown that tumors with defects in the homologous recombination (HR) pathway show improved response to DNA-damaging agents. To identify tumors likely to benefit from these therapies, we developed a 3-biomarker HR deficiency (HRD) score that is the sum of three independent measures of HRD (loss of heterozygosity (LOH), telomeric-alliclal imbalance (TAI), large-scale state transitions (LST)). Previous studies have shown that the HRD score is a better prognostic marker of OS and OS relative to the individual scores in platinum treated SOOC. Here we evaluate the correlation between, and specificity of, the 3-biomarker HRD and individual scores to quantify potential false positive and negative results.

Methods: An HRD threshold (≥32) was developed in a training cohort of ovarian and breast tumors using a cut-off of 95% sensitivity to detect BRCA1/2 deficient tumors. A threshold for each HRD component was determined using the same cohort and method (LOH ≥28, TAI ≥10, LST ≥18). The correlation between the dichotomized scores (high, low), and specificity for classifying tumors as BRCA1/2 deficient tumors, for the HRD score and component scores was retrospectively evaluated in 859 SOC tumors.

Results: The correlation between the HRD score and the LOH score was 0.872. There were 126 discordant scores, including 102 cases with high LOH scores and low HRD scores. These represent potential false positives based on LOH alone. Similarly, 24 samples with low LOH scores had high HRD scores (potential false negatives). Similar behavior was observed for TAI (correlation coefficient 0.905, 95 deficient scores) and LST (correlation coefficient 0.941, 88 discordant scores). Specificity was highest for the HRD score in both the training and test cohorts (0.897 and 0.796) compared to any of the component scores (LOH: 0.624 and 0.668, TAI: 0.766 and 0.690, LST: 0.759 and 0.672).

Conclusions: Here we show that the use of a single HRD biomarker may misinform treatment decisions in SOC relative to the combined 3-biomarker score. The combined HRD assay, which has been validated on FFPE SOC tumor tissue, warrants evaluation in a prospective study sample set in a rigorously validated laboratory.

Legal entity responsible for the study: N/A

Funding: Myriad Genetics, Inc

Characteristics of homologous recombination deficiency (HRD) in paired primary and recurrent high-grade serous ovarian cancer (HGSOC)

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Background: Recently, a 3-biomarker homologous recombination deficiency (HRD) score has been shown to predict response to DNA damaging therapies in patients with HGSOC, where patients with a high HRD score (≥242) and/or BRCA1/2 mutation show improved response. In order to evaluate whether changes in tumor biology can impact the prognostic value of this HRD score, we investigated the characteristics of HRD in paired primary and recurrent HGSOC specimens.

Methods: HRD scores were evaluated in paired primary and recurrent specimens of HGSOC from 55 patients treated with adjuvant carboplatin and paclitaxel. BRCA1/2 mutation and BRCA1 methylation (including loss of heterozygosity [LOH]) status, and HRD scores were characterized using tumor DNA-based assays.

Results: Here we present the results of the initial analysis performed for the first 25 patients. Data for 19 complete primary-recurrent pairs were available for comparative analysis (7/30 samples failed HRD analysis). HBCA mutations were detected in 12/35 (34%) of tumors, all of which occurred in BRCA1 and contained LOH at BRCA1. There was no mutation reversion in recurrent samples. Overall, 9 primary-recurrent pairs had high HRD scores, including all 3 mutant pairs. There was a high degree of correlation for all HRD scores in primary and recurrent samples (Pearson correlation coefficient 0.955). Scores for recurrent tumor samples were somewhat more likely to be higher than in the primary (mean = 2.6), but the difference was not significant (p-value = 0.11). The complete analysis will include data from paired primary and recurrent tumors from an additional 30 patients. This will allow more thorough investigation of how changes in the genomic profile of primary and recurrent tumors may impact the HRD score.

Conclusions: Here we show that the 3-biomarker HRD score was not impacted by changes in the genomic profile of primary and recurrent tumor samples. This suggests that testing recurrent HGSOC tumors will not alter treatment strategies relative to analysis of the primary tumor. Additional analysis will reveal whether the trends observed in this initial analysis are maintained in a larger cohort.

Legal entity responsible for the study: N/A

Funding: Myriad Genetics


Prognostic biomarkers in locally advanced cervical cancer (Cx Ca) treated with chemoradiation (CRT)

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Background: Definitive chemoradiation (CRT) is standard therapy for locally advanced cervical cancer (Ca). However, there is a lack of biomarkers to identify patients at increased risk of relapse. Post-treatment biopsy samples of tumour tissue may no longer show evidence of the constitutive genetic alterations that occur during tumorigenesis or during the response to treatment. The initial goal of this study was to identify markers of aggressive behaviour that could be used to predict patient outcome.

Methods: Ninety-one samples (55 primary and 36 recurrent specimens) were subjected to whole-genome sequencing (WGS) for comprehensive profiling of DNA sequence alterations. The samples were divided into two groups based on their histological characteristics: adenocarcinoma and squamous cell carcinoma.

Results: A total of 11,941 germline and 13,756 somatic variants were identified in the primary and recurrent specimens, respectively. A significant proportion of these variants were detected in genes involved in DNA repair pathways, including those involved in homologous recombination (e.g., BRCA1 and BRCA2). In addition, high levels of intratumoral heterogeneity (ITH) were observed, with a median of 73% of cells showing ITH.

Conclusions: The results of this study suggest that the genetic landscape of locally advanced cervical cancer is complex and dynamic, with significant genetic alterations occurring post-treatment. The identification of specific biomarkers could potentially guide personalized treatment strategies.

Legal entity responsible for the study: N/A

Funding: Myriad Genetics

Disclosure: Y. Kunigayan, S. Deb, R. Young, M. Blessell, L. Miedshin, D. Rischin

Correlation of mutant P53 protein expression and Ki67 index with tumor response to concurrent chemoradiation in locally advanced head and neck cancer

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Background: Concurrent chemoradiotherapy (CRT) remains the mainstay of management in locally advanced head and neck squamous cell carcinomas. Despite advancements in treatment delivery, there is heterogeneity in treatment outcome and only marginal improvement in survival rates. This study was done to find out the correlation of mutant P53 protein expression and Ki67 index with the tumor response to concurrent chemoradiotherapy.

Methods: 55 patients of stage III-IVA non-nasopharyngeal head and neck squamous cell carcinoma were enrolled and the expression of mutant P53 protein and Ki67 index in the tumor were analyzed. All patients were treated with concurrent chemoradiotherapy using conventional planning to a dose of 66 Gy in 33 fractions and 2 cycles of 1 Inj Ciklinatum 100mg/m2 as concurrent chemotherapy. The duration of mutant P53 protein expression and Ki67 index were correlated with the response to concurrent chemoradiotherapy, examined within three months of treatment completion with RECIST 1.1 criteria.
Results: It was observed that 30 patients had complete response and 25 patients had partial response to CRT. It was found that 76% of the study patients had mutant p53 protein expression and 95% had Ki67 positivity. On statistical analysis it was found that the expression of mutant p53 protein and Ki67 index showed strong association with N stage, TM stage and tumor response following CRT. All patients whose tumors were negative for mutant p53 protein expression and negative Ki-67 had complete response to CRT.

Conclusions: Rate of mutant p53 protein expression and Ki67 were significant in predicting tumor response to CRT. With careful evaluation and molecular prognostication of all head and neck cancer, high risk patients can be identified, who tend to show partial response to CRT. This might provide a cohort of patient selection for future treatment and targeted therapy against these molecular markers.

Legal entity responsible for the study: Priya Baskaran Shanmuga

Funding: VMMC and SH hospital

Disclosure: All authors have declared no conflicts of interest.

Evaluation of tumor- and stromal immune marker heterogeneity in non-small cell lung cancer

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Background: Immunotherapy is the current standard in-line treatment for non-small cell lung cancer (NSCLC) patients. However, accurate identification of patients who benefit based on immune marker (IM) expression remains a challenge. Here, we aimed to estimate the potential impact of heterogeneity on the assessment of IM expression in both adenocarcinoma (ADC) and squamous-cell carcinoma (SCC).

Methods: A total of 144 surgically treated NSCLC patients were included, 94 ADCs and 50 SCCs. Two tumor cores per patient were incorporated into tissue microarrays (TMA). CD3 and CD8 were assessed by immunohistochemistry (IHC) and PD-L1 by IHC and FISH. Expression of IM was analyzed both in tumor cells (TC) and tumor stroma (TS): A PD-L1 positivity threshold of ≥1% was established for IHC and PD-L1 gene amplification was defined as a PD-L1/CPS9 ratio of ≥2. In each core, CD3 and CD8 positive cells were counted quantitatively and the CD8/CD3 ratio was calculated. Heterogeneity of IM between corresponding tumor cores was analyzed using kappa agreement index. Finally, IM expression was correlated with clinical, pathological and molecular variables.

Results: Patients’ median age was 65, 80% were male and 46% were current smokers. PD-L1 was expressed in TC and TS in 22% and 62% of cases, respectively. Amplification of PD-L1 was found in 12 of cases, of which 8 (67%) were IHC PD-L1 positive in TC. Heterogeneity of TC PD-L1 positivity was 8% in ADC and 6% in SCC. Regarding TS PD-L1 expression, discordance between corresponding cores was found in 19% and 34% of ADC and SCC cases, respectively. PD-L1 amplification was discordant between cores in 5 of 12 (42%) cases. For each core, median CD3 and CD8 positive cells were 436 and 159, respectively. Median CD3/CD8 ratio was 0.23 in ADC and 0.53 in SCC. Taking these values as cut-off points, CD3/CD8 ratio was discordant in 22% and 10% of ADC and SCC cases, respectively. Finally, TC PD-L1 expression was correlated with CD8 (p < 0.05 for ADC and SCC).

Conclusions: PD-L1 IHC expression appears to be more heterogeneous when assessed in the TS compared to the TC compartment, especially in SCC histology. Intra-tumor heterogeneity has to be taken into account when selecting patients for immunotherapy based on tumor progression or lymphocyte presence.

Legal entity responsible for the study: University Hospital del Mar, Barcelona, Spain

Funding: Medical Oncology Department, University Hospital del Mar, Barcelona, Spain

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Hypoxonemia and hyperalumminemia as predictive factors for response to first line treatment for metastatic non-small cell lung cancer

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Background: There is a great controversies in the choice of the best drug for first line treatment of metastatic non-small cell lung cancer (NSCLC), especially for those patients with no driving mutation. In this analysis we aim to identify predictive factors which may help in selection of first line therapy for metastatic NSCLC in big retrospective data.

Methods: We conducted a retrospective analysis of patients with stage IV NSCLC receiving systemic treatment at the University of Alabama at Birmingham (UAB) comprehensive cancer center which is a NCCN member institute. Pretreatment risk factors including age, race, gender, presenting symptoms, histological feature of tumor and pretreatment laboratory values, were evaluated. These factors correlated with response to first line therapy.

Results: 409 patients received more than 10 different regimens as first line treatment in metastatic non-small-cell lung cancer. The most commonly used regimens were paclitaxel and carboplatin with or without bevacizumab; Carboplatin and gemcitabine, or Tyrosine kinase inhibitor. Most of patients in our series had performance status range between 0-1. More than 50 pretreatment factor were analyzed of which smoking (p = 0.049), pleural metastases or effusion (p = 0.004), abdominl metastases (p = 0.033), hypoaalbuminemia (p = 0.043) and hyponatremia (p = 0.062) are associated with poor responses to first line therapy against these molecular markers.

Legal entity responsible for the study: UAB

Funding: Ministry of Higher Education, Egypt

Disclosure: All authors have declared no conflicts of interest.

NGS for precision medicine in non-small cell lung cancer: Challenges and opportunities

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Background: Recent advances in target therapy development and precision oncology researches has led to the spreading of the use of the molecular testing. The need on broad tumor profiling has been met by the NGS, though several limitations remains unsolved. Methods: FFPE tissue sections were obtained from 25 patients with NSCLC (stages III-IV). DNA libraries were prepared with the Truseq Cancer Panel (Illumina). Bowtie-2 with the following Varscan2, Strelka and Scapcll accompanied with the in-house software as well as Somatic Variant Caller (Illumina) were used for data analysis.

Results: Clinically-actionable mutations were identified in 13 patients (52%). Of them 8 has activating EGFR mutations. Rare EGFR exon 19 insertion was identified in one patient, which may be associated with EGFR TKI sensitivity. This mutation was not detected employing the default software (Illumina Somatic Variant Caller) due to misalignment near the end of the reads and was successfully identified with custom pipeline. Another patient with EGFR G719 mutation harbored frameshift mutation in the 717th codon, which would eliminate EGFR activation by G719 mutation. In this case detection of siggle G719 mutation would falsely indicate at EGFR TKI sensitivity. Despite the absence of matched normal tissues we were able to detect CNV employing bootstrapping, allowing to detect EGFR amplifications in two patients. Low prevalent mutations were enriched with the C/T and G/A changes which are known to be FFPE artefacts. Therefore, mutations with allele frequency lower 10% were not detectable in 13 samples (52%). In four patients low library concentration led to the increased count of high prevalent mutations. This resulted in false positive mutations including AKT1 E17K and CTNNB1 S45F, suggesting that simple mutant allele frequency cutoff can not be used to sort out FFPE artefacts.

Conclusions: NGS allows to detect rare mutations associated with TKI sensitivity which often remain unseen using gold standard methods. Obaining low-negative information it allows to exclude false positive and false negative results. Though thinformatic pipelines remains the major sensitivity limiting stage. We were able to perform thorough configuration complexed with internal devepments to overcome these obstacles.

Legal entity responsible for the study: Vladislav Mileyko

Funding: Ministry of Education and Science of the Russian Federation (RFMEFI60717X0098)

Disclosure: All authors have declared no conflicts of interest.

Detection of early genetic and epigenetic alterations in NSCLC by using mass spectrometry and pyrosequencing analysis

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Background: Complete surgical resection remains the best curative treatment for patients with stage I non small cell cancer (NSCLC), but despite tumor resection, a high proportion of patients is still at high risk for cancer related death. Thus, there is...
a strong need of reliable biomarkers for providing information about the molecular events that occur in early stage of NSCLC.

Methods: We analyzed a ten-year series of 167 consecutive formalin fixed stage I NSCLCs. We included 67 squamous cell carcinomas (SCC) and 100 adenocarcinomas (ADC). Mutation analysis of 10 genes involved in NSCLC (EGFR, KRAS, BRAF, PIK3CA, NRAS, ALK, ERBB2, DD2, MAP2K1 and RET) was performed by MALDI-TOF Mass Spectrometry (MassARRAY, Agena Bioscience) using the Hiroyap Lung Status Kit (Diatech Pharmacogenetics). Tumor LINE-1 methylation status was determined by PCR-pyrosequencing on bisulfite-treated DNA and compared with normal lung tissue.

Results: In ADCs we identified 29 KRAS (29%), 17 EGRF (17%), two BRAF (2%) and one PIK3CA mutations (1%). Considering the smoking habit, we observed that all the KRAS mutations clustered in NSCLC from smoker patients. The never-smoker group only showed EGRF mutations. In SCCs, we identified four non-canonical mutations in EGRF gene (6%) and four mutation in PIK3CA (6%). NSCLC showed methylation levels ranging from 14.8% to 78.8% while normal tissue had percentages from 66% to 76.4%. The mean LINE1 methylation value was significantly lower in NSCLC than in normal lung (p = 0.0025). A strong LINE1 hypomethylation was observed in SCC compared with ADC samples (p < 0.0001). Moreover, a positive association between LINE1 hypomethylation and smoking habit was observed (p = 0.0003).

Conclusions: The mutation pattern typical of advanced disease is observed also in stage I NSCLC patients who may deserve tailored adjuvant therapy. LINE1 hypomethylation occurs early in NSCLC and is specifically associated with smoking habit and with SCC histology. Genetic and epigenetic events represents two complementary mechanisms in cancer and the knowledge of both types of alterations in NSCLC opens the possibility of new combinations of therapeutic agents.

Legal entity responsible for the study: University of Insubria

Funding: University of Insubria

Disclosure: All authors have declared no conflicts of interest.

References:

Screening of significant oncogenic changes in air pollution-related lung cancer in a Xuanwei County, China

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Background: Air pollution-related lung cancer has been considered as an exacerbating public health problem worldwide, particularly in developing countries. Xuanwei and Fuyuan County in Yunnan, China, regions with severely polluted air and exceptionally high lung cancer rates, are considered as good models to study air pollution-related lung cancer. This study was aimed to establish a sample and sensitive test to define the status of clinically significant oncogenes in air pollution-related lung cancer.

Methods: This study investigated the expression and mutation of HER2, and fusion gene EML4-ALK. CD74-ROS1 prevalence in lung cancer patients by reverse transcription PCR (RT-PCR) and DNA sequencing.

Results: Of the 82 patients with non-small cell lung cancer, 20.7% (17/82) exhibited HER2 up-regulation, and 1.2% (1/82) harbored HER2 insertion at exon 20. HER2 overexpression was not associated with air pollution levels and smoking status. 6.1% (5/82) showed ALK gene rearrangements, two belonged to EML4-E2 + ALK-E20 and three were EML4-ALK-E20, 3.6% (3/82) carried the CD74-ROS1 fusion gene (CD74 Ex6 + ROS1 Ex4), 3.6% (3/82) had CD74-ALK fusion found associated with smoking or a heavily polluted region, while CD74-ROS1 fusion occurred more frequently in non-smokers and in low polluted areas.

Conclusions: The screening of HER2 overexpression and EML4-ALK fusion is helpful to guide treatment of air pollution-related lung cancer; the proposed RT-PCR-based test could be a useful tool in clinical applications to screen these genetic changes.

Legal entity responsible for the study: N/A

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References:

Clinical efficacy of HER3 partners’ inhibitors in ERBB3 mutated breast cancer patients

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Background: Mutations affecting ERBB3 are rare but diffuse across cancer types. Besides the case report of an effective treatment by HER2 double blockade in an ERBB3 mutated breast cancer patient, the clinical efficacy of treatments targeting ERBB3 mutations remain largely unknown. The objective of our study was to evaluate the efficacy of approved HER3 partners’ inhibitors in the ERBB3 mutant population.

Methods: We retrospectively evaluated the clinical efficacy of HER3 partner’s inhibitor in ERBB3 mutant tumors. ERBB3 mutations were detected using Targeted Gene Panel Sequencing in patients enrolled in our molecular screening program (MOSCATO 01).

Results: Mutations in ERBB3 were observed in less than 2% of the cases (12 patients) in various tumor types: head and neck SCC (2), biliary tract carcinoma (2), a rectal neuroendocrine tumor, an uterine bladder carcinoma, a clear cell adenocarcinoma of the cervix, a carcinoma of unknown primary, a lung SCC, an invasive lobular breast carcinoma and a pterygoid sarcoma. Overall, 7 patients received HER3 partners’ inhibitors (trastuzumab + lapatinib or dabrafenib + alimemtuximab). 4 patients received other molecularly targeted agents (mTOR, PI3K or NOTCH inhibitors) and one failed being treated. We observed 1 partial response (PR) with the association of trastuzumab + lapatinib for a biliary tract carcinoma patient and 1 PR for a HNSCC patient with tonsil. Out of 6 patients with stable disease (SD), the breast cancer patient had 504 days on xeloda + lapatinib association, and the lung SCC patient had 420 days on dabrafenib. When the mutation was located in the tyrosine kinase domain (TKD), patients were highly sensitive to HER3 partners’ inhibitors, compared to mutations out of the TKD (hazard ratio for PFS = 6.63; p value = 0.01). Conversely, poor treatment efficacy was associated with the following parameters: mutations in the extracellular domain, >2 coexisting driver alterations, and > 1 previous systemic treatment line.

Conclusions: This preliminary data supports the role of ERBB3 as an oncogenic driver. Larger cohorts of patients with ERBB3 mutations will be required to further identify and validate characteristics that drive sensitivity to HER3 partners’ inhibitors.

Legal entity responsible for the study: Gustave Roussy Cancer Campus

Funding: Gustave Roussy Cancer Campus

Disclosure: All authors have declared no conflicts of interest.

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Background: STAT3 is a constitutively activated transcription factor in several cancers. In patients with mCRC overexpression of STAT3 is associated with worse survival. To determine if STAT3 is a potential target for therapy and to evaluate expression through metastatic progression in mCRC; the concordance of expression in primary and metastatic tumors was assessed.

Methods: Patients treated at the Ottawa Hospital from 2001-2012 were retrospectively identified and included if tumor tissue was available from both the primary and a metastasis. Tissue microarrays were constructed using 2 x 2mm cores for each tumor. In patients with mCRC overexpression of STAT3 is associated with worse survival. To determine if STAT3 is a potential target for therapy and to evaluate expression through metastatic progression in mCRC; the concordance of expression in primary and metastatic tumors was assessed.

Methods: Patients treated at the Ottawa Hospital from 2001-2012 were retrospectively identified and included if tumor tissue was available from both the primary and a metastasis. Tissue microarrays were constructed using 2 x 2mm cores for each tumor. Nuclear phosphorylated STAT3 expression intensity by immunohistochemistry was evaluated by 2 independent pathologists as (absent), 1-2 (low), or 3 (high). The primary outcome was concordance of STAT3 expression between primary and metastatic sites. Secondary outcomes included correlation of STAT3 expression with demographic and disease characteristics as well as clinical outcomes.

Results: Among 38 patients identified 52% were male, median age at diagnosis was 61, and 36% of metastases were synchronous. Expression of STAT3 in primary tumors was 5% high, 42% low and absent in 53% compared to 16% high, 47% low, and 37% absent in metastatic samples. Expression between paired primary and metastatic samples was concordant in 33% of patients whereas it increased in 21% and decreased in 45%. A weak correlation was observed between primary and metastatic STAT3 expression (Pearson’s correlation 0.1). After a median follow-up of 13.1 years, 30 of 35 patients included in the survival analysis died. Median survival was 4.6 years. Higher STAT3 expression in primary tumors showed a trend towards worse survival (HR 1.7, 95% CI 0.81-3.64, p = 0.01), while there was no prognostic correlation of STAT3 expression in metastases.

Conclusions: In patients with mCRC there was low concordance of STAT3 expression in primary and metastatic tumors. STAT3 expression in the primary, but not the metastatic site, was related to survival, indicating that the prognostic value of STAT3 depended on tumor sampling. These results have important implications for further research in the use of STAT3 as a biomarker in patients with mCRC.

Legal entity responsible for the study: Ottawa Hospital Research Institute

Funding: The Ottawa Hospital Department of Medicine

Disclosure: All authors have declared no conflicts of interest.
Background: HIC1 (Hypermethylated in Cancer 1) is a transcription repressor, which cooperates with several partners to suppress the expression of multiple target genes. Among HIC1 targets, SIRT1 (Sirtuin1) plays a critical role in promoting the nucleotide excision repair (NER) pathway, which is the main oxaliplatin-induced damage repair system. HIC1 expression might be influenced by the number of variations in a randomly-repeated sequence, situated close to the promoter region. We tested the hypothesis that variable number of tandem repeat (TR) in HIC1 would be associated with outcome in metastatic colorectal cancer patients (mCRC pts) receiving 1st-line chemotherapy with oxaliplatin.

Methods: This study enrolled 3 independent cohorts. Pts treated with FOLFOXIRI + bevacizumab in the phase III TRIBE study served as a training set (TRIBE-B cohort, n = 218). Pts receiving FOLFOXIRI + bevacizumab in the phase II MOMA study served as a validation set (MOMA cohort, n = 176). Pts treated without oxaliplatin (FOLFOXIRI + bevacizumab) in the TRIBE study served as a control set (TRIBE-A cohort, n = 215). Genomic DNA was isolated from blood samples. Variations in the number of TR were analyzed by PCR and Gel electrophoresis, and tested for the association with PFS and OS.

Results: Main patients characteristics were the following: TRIBE-A: M/F 60/40%, median age 60, TRIBE-B, M/F 60/40%, median age 60, MOMA, M/F 57/43%, median age 61. Median follow-up times were 49.9, 48.0, and 25.3 months, respectively. Pts with number of TR ≥4 or ≥5 were 90/10% (TRIBE-A), 91/9% (TRIBE-B), and 95/5% (MOMA), respectively. In the training cohort, pts with TR ≥5 showed a significantly higher PFS than those with TR ≤4 (95.9% vs. 91.6%, HR 1.93, P = 0.012), which retained clinical significance in multivariate analysis (HR 2.3, 95% CI 1.13-5.34, P = 0.018). This preliminary association was confirmed in the validation cohort, and pts with TR ≥5 showed a worse PFS compared to others (79.9 vs 98.0, HR 1.85, P = 0.044). This correlation was not observed in the control cohort.

Conclusions: Our findings suggest that variable number of TRs in HIC1 could be a predictive marker for oxaliplatin-containing chemotherapy in mCRC pts. Legal entity responsible for the study: University of Southern California. Funding: National Institute of Health. Disclosure: All authors have declared no conflicts of interest.

Levels of miR-17, miR-21, miR-29a and miR-92 as recurrence markers after adjuvant chemotherapy in Nx lymph node status colon cancer patients

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Background: The benefit of adjuvant chemotherapy in II and III stage patients with colon cancer (CC) is determined in large-scale trials. Despite the surprisingly large number of Nx cases (less than 12 lymph nodes examined), the potential benefit of adjuvant chemotherapy is not known and there are only a few biomarkers that could predict recurrence of the disease. Recent evidence suggests that microRNAs are important cancer markers.

Methods: CC patients (n = 18) with Nx lymph node status, who have undergone radical surgery and have completed 5-FU based adjuvant chemotherapy were included. Serum after last cycle of adjuvant chemotherapy was obtained and patients were followed-up regularly for 1 year of follow-up. Real-time reverse transcription quantitative polymerase chain reaction was used to measure the expression levels of miRNAs (miR-17, miR-21, miR-29a and miR-92), in the patients' samples and in 7 healthy individuals, as a control group.

Results: Seven patients from the tested group experienced recurrence 1 year of follow-up. Within the Nx patients all miRNAs except miR-29a had significant differences in expression levels between the recurred patients vs non recurred patients groups. The area under the receiver operating characteristic curve (AUCs) used to evaluate the predictive performance of the miR-17, miR-21, miR-92 for Nx recurred patients were 0.844, 0.948, and 0.935, respectively (p < 0.05). In Nx patients with disease only expression levels of miR-29a were not good enough to discriminate between patients with recurrence and no recurrence of the disease.

Conclusions: This study suggests that the expression levels of the tested serum miR-21, miR-17 and miR-92 in Nx patients with CC who underwent radical surgery and adjuvant chemotherapy may have diagnostic value for differentiating between recurred and non-recurred patients. Legal entity responsible for the study: Ivan Donev. Funding: Medical University Varna. Disclosure: All authors have declared no conflicts of interest.
Results: Of 105 reviewed articles, 6 were deemed suitable for review, with a total population of 283 patients underwent statistical meta-analysis. Immuno-histochemically detected hENT1 expression is found to be significantly associated with both univariate FPs (0.4395% CI: 0.31-0.69, 7% CI; Z Score = 5.16, p = 0.00001) and univariate OS (0.50495% CI: 0.38-0.67, 7% CI; Z-score = 4.75, p = 0.00001).

Conclusions: This meta-analysis demonstrates empirical evidence that hENT1 expression is a valid predictor of survival for patients undergoing gemcitabine-based chemotherapy. The hENT1 biomarker should be used to stratify patients into appropriate adjuvant chemotherapy regimens to improve outcomes and reduce unnecessary exposure to inefficacious treatments for patients determined to be hENT1-re.

Legal entity responsible for the study: Lund University, Create Health, Dept. of Immunotechnology

Funding: Lund University, Create Health, Dept. of Immunotechnology

Disclosure: L. Deahl Mellby, A. Holmér: Employee at Immunovia AB. All authors have declared no conflicts of interest.

LOSP Novel genetic marker of diarrhea in renal cell carcinoma patients treated with sorafenib

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Background: Sorafenib, the first oral anti-angiogenic multikinase inhibitor, is primarily used in the treatment of advanced renal cell carcinoma (RCC), hepatocellular carcinoma, and thyroid cancer. Common toxicities experienced by patients treated with sorafenib limiting its use and affect adherence to treatment, reducing sorafenib efficacy. No biomarkers are currently available to identify patients at risk of toxicity.

Methods: Metastatic RCC (mRCC) patients (n = 153) treated with sorafenib, as part of the TARGET study (Escudier B, N Engl J Med. 2007), were genotyped for common germline DNA variants in 56 candidate genes. Associations between 5846 variants and grade 2-4 toxicities were analyzed. Patients treated for ≥ 28 days were excluded. Toxicities included diarrhea, hypertension, hand-foot skin reaction, and/or rash or desquamation. For each toxicity, the worst grade event for each patient was used. After linkage disequilibrium-based pruning, 685 variants were utilized for analysis via a chi-squared test.

Results: Out of 153 patients, 28 (18%) experienced grade ≥ 2 diarrhea. The A allele of rs917881 (G > A) in the epidermal growth factor receptor (EGFR) gene was associated with an increased risk of grade ≥ 2 diarrhea (p = 0.00006, p = 0.04 after Bonferroni’s correction, odds ratio 3.6). The frequency of grade ≥ 2 diarrhea was 50% (3/6) in AA, 33% (15/45) in GA, and 10% (10/102) in GG patients. The frequency of grade 3 diarrhea was 8% (4/51) in patients with the A allele (AA + GA) versus 2% (2/102) in patients with the GG genotype. No other variants were significantly associated with sorafenib toxicity after Bonferroni correction.

Conclusions: To our knowledge, this is the first reported study of a genetic basis of sorafenib toxicity. rs917881 is a common intronic variant (17% allele frequency) in EGFR, RAF kinase, a critical component of the EGFR signaling pathway, is a known target of sorafenib. Patients with the rs917881 A allele treated with sorafenib may be at an increased risk for diarrhea as a result of decreased EGFR expression potentiated by sorafenib-induced inhibition of the RAF/MEK/ERK pathway, which regulates chloride secretion (Keely SJ, J Biol Chem. 1998). Replication analyses in additional patient cohorts and functional studies are ongoing.

Clinical trial identification: NCT00733307

Legal entity responsible for the study: University of North Carolina at Chapel Hill

Funding: National Institutes of Health

Disclosure: C. Pena: Employee of and owns stock in Bayer Healthcare Pharmaceuticals. All other authors have declared no conflicts of interest.

135P Molecular pathology of the 10q23.3-26.3 chromosome region in glioblastoma

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Background: Glioblastoma is the most common and aggressive primary brain tumor in adults. The most common genetic alteration in glioblastoma is the loss of heterozygosity (LOH) of the chromosome 10q. However LOH merely reflects allelic imbalance in the area without detailed information on the gene copy number.

Methods: We have been the first to conduct a targeted analysis of LOH at the 10q23.3-26.3 chromosome region which contains candidate genes PTEN, EGFR2, MK267 and MGMT in glioblastoma. A panel of microsatellite markers to detect LOH in the area under study, which includes 20 microsatellite polymorphisms, has been developed and characterized. In order to assess copy number alterations at the 10q23.3-26.3 region in glioblastoma samples with identified LOH, we have developed a system for quantitative microsatellite analysis (QMa). QMa is based on
amplification of microsatellite loci that contain (CA)n repeats where the repeat itself is the target for hybridization by the fluorescently labeled probe. The reference pool contains primer pairs for six genomic regions located on different chromosomes in which copy number variations are not typical for glioblastoma.

**Results:** Frequency of LOH at the 10q23.3-26.3 region evaluated in glioblastoma samples equals 62.1% (77/124). In 37.5% (24/64) of the samples only one copy of 10q23.3-26.3 chromosome region was found (deletion), in 25.0% (16/64) two copies were detected (acquired uniparental disomy, aUPD). In 37.5% (24/64) of the sample areas of alternation of deletion and aUPD throughout the tested region were identified. Higher frequencies of deletions were characteristic for the proximal part of 10q23.3-26.3 region (PTEN and FGFR2 genes), while aUPDs were more frequent in the distal part (MGMT gene). Thus, the transition from a region with deletion to a region with aUPD occurs at 10q26.1 - 10q26.2.

**Conclusions:** Thus, we have shown that the LOH at the 10q23.3-26.3 region in glioblastoma can reflect either a deletion or an aUPD. Detailed study of copy number changes at the 10q23.3-26.3 chromosome region containing PTEN, FGFR2, MGMT and MLH1 will allow to discover new targets for drugs and molecular markers of disease prognosis and response to therapy.

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**Disclosure:** All authors have declared no conflicts of interest.

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**Abstracts**

**103P**

Using diffusion-weighted MRI derived apparent diffusion coefficient as a predictive biomarker of tumor response in non-Hodgkin lymphoma

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**Background:** Diffusion-weighted MRI (DW-MRI) is a radiation free, non-invasive diagnostic imaging technique detecting random movement of water molecules in vivo. Extent of diffusion in fluids and tissues can be assessed quantitatively using apparent diffusion coefficient (ADC). The aim of this study was to determine usefulness of DW-MRI with ADC calculation for early prediction of tumor response in patients with non-Hodgkin lymphoma (NHL).

**Methods:** DW-MRI was performed in 26 patients (13 males and 13 females, mean age 55 years, range 26-76) with NHL at baseline, after 1 cycle and at the end of induction chemotherapy. The largest necrotic lymph node was chosen as a target lesion for DW-MRI with ADC calculation for early prediction of tumor response in patients with non-Hodgkin lymphoma (NHL).

**Results:** Target lesion ADC (mean ± SD) increased from 0.81 ± 0.33 × 10⁻³ mm²/s to 0.65 ± 0.15 × 10⁻³ mm²/s predicted CR at baseline to 1.16 ± 0.44 × 10⁻³ mm²/s after 1 cycle of chemotherapy resulting in average increase of 36.4 ± 22.0%. Pre-treatment ADC was significantly lower in patients with CR than in patients with PR – 0.63 ± 0.15 × 10⁻³ mm²/s and 0.94 ± 0.39 × 10⁻³ mm²/s respectively (p = 0.03). Pre-treatment ADC ≥ 0.88 × 10⁻³ mm²/s predicted CR with a sensitivity of 100%, specificity of 50% and accuracy of 77%. When two parameters were combined prediction accuracy increased to 83%.

**Conclusions:** DW-MRI with ADC calculation can be used for pretreatment and early during treatment tumor response prediction in patients with NHL. Combination of pretreatment ADC and ADC change post 1 cycle of chemotherapy increases prediction accuracy.

**Legal entity responsible for the study:** N.N. Alexandrov National Cancer Centre of Belarus

**Funding:** Ministry of Health

**Disclosure:** All authors have declared no conflicts of interest.

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**104P**

Identification of an epigenetic biomarker predicting the response to therapy with APG101 in glioblastoma

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**Background:** APG101, a fully human fusion protein consisting of the extracellular domain of CD95L and the Fc domain of IgG1, has been developed by Apogenix AG and was confirmed as a potent inhibitory of CD95L-induced invasion of glioblastoma cells in vitro. In a randomized phase 2 study in glioblastoma patients with 1st or 2nd relapse the combined therapy of APG101 plus radiotherapy (RT) was found to be superior to RT alone in a clinically relevant order of magnitude in all efficacy endpoints (i.e. PFS, PFS and OS). At the same time APG101 exhibited an excellent safety profile and was well tolerated. The presented data summarizes the identification of a predictive biomarker.

**Methods:** To identify potential biomarkers we used available tissue sections originating from archived primary tumor of the study patients and analyzed them for the expression of CD95L as well as for the DNA methylation status.

**Results:** A genome-wide assessment of DNA methylation identified a single CpG-site (CpG2) upstream of the CD95L-promoter that showed differential methylation between APG101 responders (PFS > 5 months) and non-responders (PFS ≤ 2 months). Available patient DNA were in addition analyzed by MassARRAY and Pyro-sequencing to confirm differential CpG2 methylation. Based on this data we used the median of the CpG2 methylation level as a threshold to analyze for a correlation of CpG2 methylation and response to APG101 therapy. Patients showing a low level of CpG2 methylation responded best to therapy with APG101 whereas patients with a high level of CpG2 methylation did not show a relevant benefit when treated with APG101 compared to the control RT-group. The analysis shows a significant survival benefit achieved in patients with low CpG2 methylation (median OS: 16.1 vs. 7.7 months, p = 0.038).

**Conclusions:** The level of CpG2 methylation in the CD95L promoter in the patients' glioblastoma tissue is a prognostic biomarker predicting response to therapy with APG101. Apogenix currently develops a qPCR-based assay to quantify CpG2 methylation. This assay is intended as companion diagnostic to identify patients that may respond best to APG101 treatment.

**Clinical trial identification:** EudraCT-Number: 2009-13421-42

**Legal entity responsible for the study:** Apogenix AG

**Funding:** Apogenix AG

**Disclosure:** M. Thiermann, C. Geifer, C. Kurz, J. Sykora, C. Merz, H. Frick: Employee of Apogenix AG. W. Wic: Commercial research grant from Boehringinger Ingelheim and Roche, speaker’s bureau honoraria from Prime Oncology; and is a consultant/advisory board member for Eli Lilly and Co. and Roche. All other authors have declared no conflicts of interest.

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**104P**

AP010 sensitivity in relapsed multiple myeloma patients


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**Background:** Multiple myeloma is the next most common hematological malignancy and represents a continuous medical challenge since all patients eventually progress despite of many new drugs approved lately. The incidence of MM is about 6 to 8 out of 100,000 in Western Countries. AP010 (a hexameric FAS-ligand) is an immune-oncologic drug, which mimics cytotoxic T-lymphocyte signaling to induce apoptosis and could therefore be an effective new drug for MM as these cells express CD95 (FAS-receptor).

**Methods:** Using a previously validated method by Medical Prognosis Institute A/S (MPI), we have developed an AP010 response predictor (AP010-DRP™), which is based on gene expression cluster obtained by comparing associations between gene expression profiles and growth inhibition by AP010 in a panel of cell lines. A second step has included filtering the identified gene expression profile against mRNA expression from a collection of 3200 human tumors, thereby making a predictive profile for AP010 responsiveness. We have initiated to screen relapsed/refractory MM patients by isolating CD138 positive myeloma cells from the bone marrow and perform AP010-DRP™ in order to select the patients with the highest likelihood of benefit from AP010 treatment.

**Results:** Using the AP010-DRP™ analysis demonstrated multiple myeloma to be sensitive to AP010 compared to most solid tumors except breast cancer, which also appeared to be sensitive. First results from multiple myeloma patient screening will be presented at ESMO 2016.

**Conclusions:** Combining AP010 with DRP™ analysis will add a prognosis medicine element to immune-oncology treatment of multiple myeloma. This will enable us to identify patients with high likelihood of response and thereby facilitate focused future trial design and patient recruitment to achieve clinical success.

**Clinical trial identification:** Danish Ethical Committee, Journal nr.: H15018326, Approved on 01/03/2016

**Legal entity responsible for the study:** Oncology Venture

**Funding:** Oncology Venture

**Disclosure:** All authors have declared no conflicts of interest.
Background: LEA Study (GEICAM/2006-11/GGB351), is a randomized clinical trial comparing bevacizumab as an endocrine therapy (ET) in postmenopausal women with advanced or metastatic HR-positive/HER2-negative breast cancer (BC) with indication of hormone therapy as first-line therapy. Patients with secondary hypertension had better progression-free survival (PFS) and overall survival (OS). We have evaluated the role of two hypertension-related biomarkers, Angiotensin-Converting Enzyme (ACE) and Small-Inducible Cytokine B10 (CXCL10) as prognostic and/or predictive biomarkers of benefit to bevacizumab in the first line metastatic disease.

Methods: From 380 patients, 266 were included in 33 Spanish sites. Median age was 64 years, 65.3% had measurable disease, 97.4% were metastatic at randomization, 55.1% had visceral disease and 52.6% received previous chemotherapy. PFS was 14.3 months (range 0.8-61.1), OS was 34 months (range 0.8-71.6) and 93 patients had Objective Response (OR). We analyzed 124 plasma samples collected before treatment (52 from ET and 72 from ET + B arms). Circulating levels of ACE and CXCL10 were determined by ELISA. ACE levels of 115mg/l and 135mg/l were pre-defined as cutoff values. CXCL10 was explored as a quantitative variable.

Results: PFS was 15.1 months (range 1.4-61.1), OS was 31.1 months (range 2.8-61.1) and the median OS of 34 months (range 0.8-71.6). OR was 3.906 (p = 0.037), indicating the contribution of this SNP to benefit of bevacizumab in the first line metastatic disease.

Conclusions: ACE levels could be considered a prognostic and a bevacizumab predictive biomarker of PFS. CXCL10 could be prognostic of OS. Confirmatory studies are warranted.

Clinical trial identification: EUDRACT 2007-002841-19
Background: The ALKA-371-001 phase 1 trial was implemented to assess safety and dosing in patients with advanced solid tumors and treated with entrectinib, which targets the tyrosine kinases encoded by NTRK1, NTRK2, NTRK3, ROS1, and ALK. Being a targeted therapy, a subset of patients were enrolled based on the local assessment of gene rearrangements in the NTRK1, ROS1 or ALK genes, by FISH or IHC, during dose escalation and expansion. Retrospectively, a subset of phase 1 patient specimens were submitted for central laboratory testing using RNA based next generation sequencing (NGS) to determine status of gene rearrangements (n = 33) of those, 23 were treated at, or above, the recommended phase 2 dose. Together, these clinical responses were correlated with the detection of a gene rearrangement to assess prediction of outcome based on patient selection.

Methods: Two primary hospital centers performed FISH or IHC for the assessment of gene rearrangements and applied consensus scoring. These results were used for patient enrollment and treated as the reference standard. For central testing, an anchored multiplex PCR NGS of sample RNA was used to assess gene rearrangements. Tumor response was determined using RECIST criteria. Statistical analyses to test correlation with outcomes were performed.

Results: For patients with results from both local testing and central confirmation testing (n = 33), there is strong negative agreement (100%) yet poor positive agreement (ALK 62.5%, ROS1, 40%, NTRK3, 50%). However, when results are correlated with n = 23 study patients with the overall response rate (PR or CR), there is strong positive agreement (100%) yet poor negative agreement. The early identification of appropriate diagnostic testing at the centrally must be readily deployable to local testing laboratories to find patients beyond 68% (1.41 mo.) than for E (2.58 mo., log-rank p = 0.03). RD was longer for I + E (7.20 mo.) than for E (4.21 mo. (log rank p = 0.36). There was no difference in PFS (4.07 mo. for I + E and 4.11 mo. for E (log rank p = 0.11)). Correlative analysis of OS and PFS with ABA levels showed that pts with baseline IgG ABA of >35 µg/mL when compared to those with <35 µg/mL achieved an increased PFS (log rank p = 0.024) and OS (log-rank p = 0.002) when receiving I + E but not when receiving E alone (log rank p = 0.40 and 0.91, respectively). These pts also showed a trend to longer PFS and OS compared to E alone (p = ns).

Conclusions: I + E did not improve OS or PFS vs. E alone. Levels of IgG ABA >35 µg/ mL correlated with a statistically significant increase in PFS and OS in pts receiving I+E, but not in those receiving E alone. Further validation studies of this Imprime PGG-specific biomarker and its correlation with clinical outcomes are warranted.

Clinical trial identification: NCT01309126

Legal entity responsible for the study: Biothera Pharmaceuticals

Funding: Biothera Pharmaceuticals

Disclosure: M. Patchen, M.A. Gargano, B. Ma, J. Lowe, J.L. Iglesias. Employee of Biothera Pharmaceuticals and receives stock options as part of her compensation. All other authors have declared no conflicts of interest.

Results: 140 pts were randomized to I + E and 77 to E. The study closed early due to low accrual. Median OS in the IIT population was 15.1 mo. for E and 10.7 mo. for I + E. (log-rank p = 0.047). Post-progression therapy was higher for E (58%) than for I + E (46%). ORR was 10% for E and 7% for I + E (p = 0.45). TTR was shorter for I + E (1.41 mo.) than for E (2.58 mo., log-rank p = 0.03). RD was longer for I + E (7.20 mo.) than for E (4.21 mo. (log rank p = 0.36). There was no difference in PFS (4.07 mo. for I + E and 4.11 mo. for E (log rank p = 0.11)). Correlative analysis of OS and PFS with ABA levels showed that pts with baseline IgG ABA of >35 µg/mL when compared to those with <35 µg/mL achieved an increased PFS (log rank p = 0.024) and OS (log-rank p = 0.002) when receiving I + E but not when receiving E alone (log rank p = 0.40 and 0.91, respectively). These pts also showed a trend to longer PFS and OS compared to E alone (p = ns).

Conclusions: I + E did not improve OS or PFS vs. E alone. Levels of IgG ABA >35 µg/ mL correlated with a statistically significant increase in PFS and OS in pts receiving I+E, but not in those receiving E alone. Further validation studies of this Imprime PGG-specific biomarker and its correlation with clinical outcomes are warranted.

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Levels of endogenous anti-beta-glucan IgG antibodies (ABA) predict clinical outcomes for imprime PGG: Evidence from phase 3 PRIMUS study in patients (pts) with metastatic colorectal cancer (mCRC)

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Background: Imprime PGG (I) is a yeast-derived beta-glucan PAMP administered systemically. It binds endogenous ABA to form immune complexes opsonized by complement, which trigger immune cell activation. Combination Ph 2 trials with monoclonal antibodies (mAbs) in over 300 cancer pts have shown increased clinical benefit, including PFS and OS, enhanced in ABA+ patients.

Methods: PRIMUS was a Ph 3, open-label, multi-center randomized study of ABA levels showed that pts with baseline IgG ABA of >35 µg/mL when compared to those with <35 µg/mL achieved an increased PFS (log rank p = 0.024) and OS (log-rank p = 0.002) when receiving I + E but not when receiving E alone (log rank p = 0.40 and 0.91, respectively). These pts also showed a trend to longer PFS and OS compared to E alone (p = ns).

Conclusions: I + E did not improve OS or PFS vs. E alone. Levels of IgG ABA >35 µg/ mL correlated with a statistically significant increase in PFS and OS in pts receiving I+E, but not in those receiving E alone. Further validation studies of this Imprime PGG-specific biomarker and its correlation with clinical outcomes are warranted.

Clinical trial identification: NCT01309126

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Disclosure: M. Patchen, M.A. Gargano, B. Ma, J. Lowe, J.L. Iglesias. Employee of Biothera Pharmaceuticals and receives stock options as part of her compensation. All other authors have declared no conflicts of interest.

Similarity-based automated evidence ranking for clinical interpretation of multigene diagnostic panels

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Background: Precision medicine incorporates individual molecular genetic profiles in cancer therapeutic decisions. Establishing clinical relevance of tumour biomarkers can be limited by distinct biomarker functions in different histology types, simultaneous presence of multiple biomarkers in different combinations, long-tail distribution of driver genetic alterations and the resulting limited number of similar cancer cases. Difficulty in aggregating definitive phase 3 trial data further hampers optimal delivery of tumour genomic information to the clinic especially in the case of rare mutations. These might result in conflicting evidence regarding biomarker roles and requires decision support algorithms to help cancer treatment decisions.

Methods: Here we describe a novel decision support system which is capable of dynamically aggregating and ranking scientific and clinical evidence to aid cancer therapeutic decisions.

Results: The algorithm aggregates scientific evidence and clinical experience for an automated, adaptive ranking of anti-cancer therapies that best match with the molecular and clinical profile of the individual patient and are supported by the most relevant evidences. Input is generated by cancer molecular profiles and clinical parameters. Outcome is represented by identification of clinically relevant tumour genetic alterations and matching drugs. Compounds are ranked based on the number and merit of scientific evidence that support the functional relevance of identified genetic alterations (biomarker or driver evidence) and their association with drug targets (target evidence) or compounds (drug evidence). Direct association between drugs and tumour histologies are also counted. Evidence is also weighted based on similarity to the given cancer case. The algorithm is used to combine and prioritize evidences based on their relevance (clinical over preclinical, direct over indirect, registered over non-registered indications) and level. Evidences are constantly updated and accumulated.

Conclusions: Incorporation of similarity-based evidence ranking in classical evidence-based medicine enhances the delivery of genomically informed precision medicine.

Legal entity responsible for the study: Oncomapse Medicine Hungary

Funding: Oncomapse Medicine Hungary

Disclosure: All authors have declared no conflicts of interest.
Background: Cytidine deaminase (CDA) catalyzes ganciclovir and cytosine arabinoside and its serum activity (CDA-A) has been associated with efficacy and toxicity of both treatments. CDA is mainly produced by hepatocytes and neutrophils. Our objective was to identify pretreatment patients' (pts) characteristics that may contribute to the large inter-individual variability in CDA-A.

Methods: From December 2014 to November 2015, all consecutive pts were prospectively included into this single-center study. CDA-A in serum was assessed using a standardized spectrophotometric method. Biological, clinical characteristics and 5 common single nucleotide polymorphisms in the CDA gene (4355 > c, 492 > g, 336 > t, 798 > A, 4769 > C) were analyzed according to pretreatment CDA-A. Written consent was obtained from all patients. Univariate and multivariate statistical analysis were performed on log-transformed CDA-A with significance level of 0.05.

Results: 275 pts (male: 61%) were analyzed. Median age was 66 years. Main primary tumor locations were lung (19%), prostate (11%) and urinary tract (10%). Median CDA-A was 4.08 U/mg (range 1.53-15.49). The inter-individual variability in CDA-A was large (43%). 49 pts (18%) had high CDA-A (> 6 U/mg). In univariate analysis, ANC status (p = .0003) and -33delC genotype (p = .0152) were associated with CDA-A. CDA-A was independently associated with ANC status (p = .0001) and -33delC genotype (p = .0152). In multivariate analysis, only ANC status was significantly associated with CDA-A (p < 10^-7). C-reactive protein level (p = 0.1), malnutrition (p = 0.014), altered ECOG performance (p = 0.016) and a history of chemotherapy (p = 0.049) were associated with high CDA-A. A logistic regression model for high CDA-A (p = 0.0152) includes ANC status (OR 5.26), BMI > 25 (OR 2.53), and ECOG performance (p = 0.016).

Conclusions: Our results show for the first time an association between the pretreatment number of neutrophils and CDA activity, suggesting a CDA release from neutrophils. However, it explains only a small part of inter-individual variability in CDA-A. Therefore, CDA-A assessment in serum remains of interest to identify pts with high risk of toxicity or low efficacy under pyrimidine analogues.

Legal entity responsible for the study: Paris Descartes University, Cochin - Port Royal Hospital, AP-HP

Funding: None

Disclosure: None

Recruitment of SerLint patients is ongoing at 7 French University Hospitals in the AP-HP, Paris, France. The 1st cohort of 45 patients (pts) was recruited and analyzed. In univariate analysis, ANC status (p = .0003) and -33delC genotype (p = .0152) were associated with CDA-A. CDA-A was independently associated with ANC status (p = .0001) and -33delC genotype (p = .0152). In multivariate analysis, only ANC status was significantly associated with CDA-A (p < 10^-7). C-reactive protein level (p = 0.1), malnutrition (p = 0.014), altered ECOG performance (p = 0.016) and a history of chemotherapy (p = 0.049) were associated with high CDA-A. A logistic regression model for high CDA-A (p = 0.0152) includes ANC status (OR 5.26), BMI > 25 (OR 2.53), and ECOG performance (p = 0.016).

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Legal entity responsible for the study: Paris Descartes University, Cochin - Port Royal Hospital, AP-HP

Funding: None

Disclosure: None

Development of an ELISA to detect tumor-associated antigen tNASP in urine

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Background: Tumor-associated antigens (TAAs) are proteins that elicit a humoral immune response when their expression is elevated in tumor progression. tNASP is one of two splice variants of Nuclear Autoantigenic Splice Protein. In addition to its normal testicular expression, it is also aberrantly expressed in cancer cells. We have previously demonstrated that immunohistochemical detection of tNASP has high diagnostic accuracy and specificity in ovarian cancer. tNASP is also aberrantly expressed in prostate cancer cells and tissues. In the current study, we developed an ELISA to detect specific anti-tNASP serum antibodies as well as tNASP protein in urine for early diagnosis of prostate cancer.

Methods: tNASP protein expression was assayed by immunohistochemistry (IHC) in prostate cancer biopsy samples from different disease stages, using affinity-purified goat anti-tNASP serum, which specifically recognizes only tNASP protein. A recombinant tNASP protein fragment was used as bait to produce a standard curve for detection of anti-tNASP antibodies by ELISA. Serum and urine samples from patients with prostate cancer, and otherwise healthy control patients, were obtained from the Tissue Procurement Facility of the University of North Carolina at Chapel Hill, Roswell Park Cancer Institute, and Fox Chase Cancer Center. Correlation between serum anti-tNASP antibody levels, urine tNASP protein level and Prostate Specific Antigen (PSA) was analyzed by Spearman's coefficient.

Results: ELISA measurements demonstrated a significant increase in tNASP protein levels in the urine of prostate cancer patients, as compared to control group urine. Spearman's rank correlation demonstrated that the concentration of anti-tNASP antibodies and tNASP levels in urine co-varied with PSA levels. Urine tNASP protein was detected by ELISA with anti-t-tNASP antibody as bait, whereas anti-tNASP antibodies were not detected in urine samples.

Conclusions: Combined detection of serum anti-tNASP antibody and urine tNASP protein could be used for diagnosis of prostate cancer and has the potential to improve early diagnostic confidence.

Legal entity responsible for the study: This study was supported by Campbell University School of Osteopathic Medicine, North Carolina, 27506, USA. Associate Professor Oleg Alekseev, MD, PhD is a principal investigator on this project.

Funding: This study was funded by School of Osteopathic Medicine of the Campbell University (CUSOM). Principal investigator Dr. Oleg Alekseev is a full-time faculty in CUSOM and research activity is his duty along with teaching.

Disclosure: All authors have declared no conflicts of interest.
Superimposable outcomes for sequential and concomitant administration of adjuvant trastuzumab in HER2-positive breast cancer: Results from the SIGNAL/PHARE prospective cohort

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Background: Several adjuvant clinical trials in early HER2 positive breast cancer have assessed either sequential or concomitant incorporation of trastuzumab with chemotherapy. Only the NCTCT-N9831 trial prospectively compared the two modalities and whether their results didn’t demonstrate a significant benefit difference, the authors have recommended the concurrent regimen with taxane chemotherapy instead of the sequential modality on the basis of a positive risk-benefit ratio. This present research assessed those two modalities sequential versus concomitant in the PHARE/SIGNAL cohort.

Methods: PHARE was a randomized phase III clinical trial (NCT00381901) and SIGNAL (RECF1998) was a prospective study specifically designed for GWAS analyses. The comparison in the HER2 positive group of adjuvant trastuzumab and chemotherapy modalities and whether their results didn’t demonstrate a significant benefit difference, the authors have recommended the concurrent regimen with taxane chemotherapy instead of the sequential modality on the basis of a positive risk-benefit ratio. This present research assessed those two modalities sequential versus concomitant in the PHARE/SIGNAL cohort.

Results: The SIGNAL/PHARE cohort included 11,728 breast cancer cases; 5,502 of them with HER2 positive tumour: 34.5% (1957/5502) were treated by sequential and 65.5% (3605/5502) by concomitant modulation of administration for taxane-chemotherapy and trastuzumab. The adjusted comparison found similar OS (HR = 1.01; 95% CI: 0.86-1.19) and similar DFS (HR = 1.08; 95%CI 0.96-1.21).

Conclusions: These results suggest that the sequential administration of trastuzumab given after the completion of adjuvant chemotherapy might be as valid as the concomitant administration of trastuzumab and taxane chemotherapy in the adjuvant setting.

Clinical trial identification: NCT00381901 & RECF1998

Legal entity responsible for the study: French national Cancer Institute (InCa)

Funding: French national Cancer Institute (InCa)


Research Unit and Medical Oncology, Alcántara University Hospital, Albacete, Spain, IRCCS for Onkologie, St. Gallen, Switzerland. Statistics, GEICAM (Spanish Breast Cancer Research Group), Madrid, Spain, Translational Research, GEICAM (Spanish Breast Cancer Research Group), Madrid, Spain, 1Research Unit and Medical Oncology, Alcántara University Hospital, Albacete, Spain, 2Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, 3Medical Oncology, Centro Oncologico de Girona, Girona, Spain, 4Medical Oncology, Hospital de Castilla, Giron, Spain, 5Serv. Hematologia y Oncologia Medica, Hospital Clinico Universitario de Valencia, Valencia, Spain, 6Medical Oncology Dept., Hospital Donostia, San Sebastian, Spain, 7GEICAM (Spanish Breast Cancer Research Group), Madrid, Spain, 8Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada, 9Medical Oncology, Canada10lstituto de Investigacion Sanitaria Gregorio Maranon, Madrid, Spain

Background: Inflammation is a hallmark of cancer. Elevated markers of host inflammation have been associated with worse outcomes in several solid tumours. Here, we explore the prognostic role of the derived neutrophil-to-lymphocyte ratio (dNLR) in subgroups of women with early breast cancer.

Methods: This was a retrospective analysis of women with early breast cancer included in the GEICAM/9906 trial, a randomized phase III study of adjuvant FEC compared to FEC-paclitaxel (FEC-P) in breast cancer patients with axillary involvement. dNLR was calculated as the ratio of neutrophils divided by the difference between total leukocytes and neutrophils measured in peripheral blood before the start of chemotherapy. The primary objective was disease free survival (DFS) and overall survival (OS) was a secondary endpoint. Univariable Cox regression was used to explore the prognostic and predictive value of dNLR (explored as median cutoff and grouped in quartiles).

Results: The current analysis comprised 1243 patients from 65 Spanish sites with a median follow-up of 10 years. Median age was 50 years (range 23-76), 66% of patients had available PAM50 subtype determination, of which 22% of the tumors were Luminal A, 21% Luminal B, 14% Her2-enriched, 6% Basal-like, and 3% Normal-like. ER/PgR and ER/PgR2 subtypes comprised 47% and 13% of evaluable tumors, respectively. Median dNLR was 1.35 (IQR 1.08 – 1.71). For Her2-enriched patients by PAM50, a >dNLR median was significantly associated with worse DFS, p = 0.003 (HR: 1.63, 95%CI 1.04 – 2.54). For non-luminal patients by PAM50, a >dNLR median and a high dNLR explored by quartiles were associated with worse DFS (p = 0.02 and p = 0.003, respectively). For patients with ER/PgR2 tumors, a high dNLR grouped in quartiles was associated with worse DFS and OS (p < 0.001 and p = 0.007, respectively).

Conclusions: dNLR is associated with worse DFS in women with Her2-enriched and non-luminal intrinsic subtypes defined by PAM50 multigene expression assay. High dNLR is also associated with worse DFS and OS in women with ER/PgR2 tumors (IHC). Further studies are warranted to confirm these findings.

Clinical trial identification: N° EudrACT: 2005-003108-12

Legal entity responsible for the study: GEICAM Spanish Breast Cancer Group

Funding: GEICAM Spanish Breast Cancer Group

Disclosure: All authors have declared no conflicts of interest.
Conclusions: This large population-based observational study of NO HR+ BC shows that unacceptably high BCSM persists in US clinical practice for pts with RS ≤ 11 and no adjuvant chemotherapy (CT). Physicians are increasingly using the BCSM estimates for treatment decisions in NO BC. We evaluated treatment and clinical outcomes in NO pts undergoing RS testing through Clalit Health Services (CHS).

Methods: Medical records of all CHS pts with NO ER+ HER2- BC who were tested with distant recurrence (DR)/BC death by Paik et al and TAILORx RS categorization and by nodal status are presented in Table. As pts were not randomized to treatment, analysis of DR/BC death by CT use is only exploratory: within the RS 18-30 group, CT-un-treated pts (60%) had DR rate and BC death rate of 9.6% and 3.7%, respectively, whereas in CT-treated pts (40%) these rates were 2.2% and 1.1%; within the RS 11-25 group, CT-un-treated pts (82%) had DR rate and BC death rate of 4.1% and 1.2%, respectively, whereas in CT-treated pts (18%) these rates were 2.7% and 0%.

Background: Recent outcome data including those from the prospective TAILORx trial strongly confirmed the RS role in node negative (NO) E2F-BC. The prospective WSG planx study showed excellent outcomes in high-risk NO and node-positive (N+) pts with RS ≤ 11 and no adjuvant chemotherapy (CT). Physicians are increasingly using the BCSM estimates for treatment decisions in NO BC. We evaluated treatment and clinical outcomes in NO pts undergoing RS testing through Clalit Health Services (CHS).

Methods: Medical records of all CHS pts with NO ER+ HER2- BC who were tested with distant recurrence (DR)/BC death by Paik et al and TAILORx RS categorization and by nodal status are presented in Table. As pts were not randomized to treatment, analysis of DR/BC death by CT use is only exploratory: within the RS 18-30 group, CT-un-treated pts (60%) had DR rate and BC death rate of 9.6% and 3.7%, respectively, whereas in CT-treated pts (40%) these rates were 2.2% and 1.1%; within the RS 11-25 group, CT-un-treated pts (82%) had DR rate and BC death rate of 4.1% and 1.2%, respectively, whereas in CT-treated pts (18%) these rates were 2.7% and 0%.

Table: 146O

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Table: 147PD

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<th>Paik et al RS categorization</th>
<th>CT use, %</th>
<th>DR rate, %</th>
<th>BC death rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS ≤18</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>N1mi (n = 146)</td>
<td>5</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>1 positive node (n = 128)</td>
<td>10</td>
<td>4.7</td>
<td>0.0</td>
</tr>
<tr>
<td>2-3 positive nodes (n = 65)</td>
<td>8</td>
<td>6.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Total (n = 339)</td>
<td>7</td>
<td>3.2</td>
<td>0.9</td>
</tr>
<tr>
<td>RS 18-30</td>
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<td></td>
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<td>N1mi (n = 93)</td>
<td>37</td>
<td>10.8</td>
<td>3.2</td>
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<td>1 positive node (n = 81)</td>
<td>47</td>
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<td>2.5</td>
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<tr>
<td>2-3 positive nodes (n = 53)</td>
<td>38</td>
<td>5.8</td>
<td>1.9</td>
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<td>Total (n = 227)</td>
<td>40</td>
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<td>RS ≥31</td>
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<td>N1mi (n = 31)</td>
<td>97</td>
<td>19.4</td>
<td>16.1</td>
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<td>1 positive node (n = 22)</td>
<td>86</td>
<td>18.2</td>
<td>13.6</td>
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<tr>
<td>2-3 positive nodes (n = 8)</td>
<td>75</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total (n = 61)</td>
<td>90</td>
<td>16.4</td>
<td>13.1</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>TAILORx RS categorization</th>
<th>CT use, %</th>
<th>DR rate, %</th>
<th>BC death rate, %</th>
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<tbody>
<tr>
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<td></td>
<td></td>
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<tr>
<td>N1mi (n = 45)</td>
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<td>2.2</td>
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<tr>
<td>1 positive node (n = 37)</td>
<td>14</td>
<td>5.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2-3 positive nodes (n = 20)</td>
<td>0</td>
<td>10.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Total (n = 102)</td>
<td>7</td>
<td>4.9</td>
<td>2.0</td>
</tr>
<tr>
<td>RS 11-25</td>
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<td></td>
</tr>
<tr>
<td>N1mi (n = 169)</td>
<td>14</td>
<td>4.1</td>
<td>1.2</td>
</tr>
<tr>
<td>1 positive node (n = 152)</td>
<td>20</td>
<td>3.3</td>
<td>0.0</td>
</tr>
<tr>
<td>2-3 positive nodes (n = 90)</td>
<td>22</td>
<td>4.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Total (n = 411)</td>
<td>18</td>
<td>3.9</td>
<td>1.0</td>
</tr>
<tr>
<td>RS &gt;25</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>N1mi (n = 56)</td>
<td>82</td>
<td>16.1</td>
<td>10.7</td>
</tr>
<tr>
<td>1 positive node (n = 42)</td>
<td>83</td>
<td>14.3</td>
<td>11.9</td>
</tr>
<tr>
<td>2-3 positive nodes (n = 16)</td>
<td>69</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total (n = 114)</td>
<td>81</td>
<td>13.2</td>
<td>9.6</td>
</tr>
</tbody>
</table>
Annals of Oncology

Conclusions: CT use was aligned with the RS results. Ps with N1mi or 1-3 positive nodes and RS ≤ 25 had very good outcomes, even when selected for endocrine therapy alone. Updated data will be presented at the meeting.

Clinical trial identification: Trial protocol number: 0075-14-COM

Legal entity responsible for the study: Dr. Stemmer is the sponsor-investigator responsible for all aspects of the study including design and conduct of the study, collection, analysis and interpretation of the data, and preparation of the manuscript.

Funding: Funded through grant from Teva Pharmaceuticals Ltd.

Disclosure: S.M. Stemmer: Received grant funding from Teva and travel expenses from Genomic Health. L. Sosun- Gutman: Teva employee. Holds stock options for Teva Pharmaceuticals Ltd. A. Bareket-Samish: Consultant for Teva Pharmaceutical Industries and Genomic Health, Inc. O. Rosengarten: Received payments for lectures and grants for traveling from Teva Pharmaceuticals. C. Svedman, S. Shah: Genomic Health employee. Holds stock options for Genomic Health. N. Ben-Baruch: Serves on Genomic Health’s speakers bureau. All other authors have declared no conflicts of interest.

Table: 149PD

<table>
<thead>
<tr>
<th>Histotype</th>
<th>Ki67</th>
<th>5-yr OS (%)</th>
<th>10-yr OS (%)</th>
<th>Log-Rank</th>
</tr>
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<tbody>
<tr>
<td>ILC</td>
<td>≤ 4%</td>
<td>96.9</td>
<td>89.9</td>
<td>p = 0.008</td>
</tr>
<tr>
<td>ILC</td>
<td>&gt; 4%</td>
<td>90.1</td>
<td>77.2</td>
<td></td>
</tr>
<tr>
<td>IDC</td>
<td>≤ 18%</td>
<td>97.4</td>
<td>95.8</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>IDC</td>
<td>&gt; 18%</td>
<td>93.6</td>
<td>62.6</td>
<td></td>
</tr>
<tr>
<td>ILC</td>
<td>≤ 4%</td>
<td>88.2</td>
<td>79.4</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>ILC</td>
<td>&gt; 4%</td>
<td>81.1</td>
<td>69.2</td>
<td></td>
</tr>
<tr>
<td>IDC</td>
<td>≤ 14%</td>
<td>96.0</td>
<td>87.0</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>IDC</td>
<td>&gt; 14%</td>
<td>89.2</td>
<td>61.8</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Despite the retrospective and exploratory nature of the study, the prognostic relevance of Ki67 (as well as its optimal cut-off) seems to significantly differ according to histology. In particular, a very low cut-off of Ki67 (4%) may significantly discriminate the prognosis of pts with ILC.

Legal entity responsible for the study: University of Verona, Verona

Funding: University of Verona, Verona

Disclosure: All authors have declared no conflicts of interest.

149PD

Analysis of Oncotype DX recurrence score and its clinical implications in invasive lobular carcinomas of the breast

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2College of Medicine, Penn State University, Penn State College of Medicine, Hershey, PA, USA.
3Oncology, Penn State Medical Center, Hershey, PA, USA.

Background: The Oncotype DX breast cancer assay is increasingly being used to guide treatment decisions for patients with early stage, hormone-positive, Her-2 negative breast cancer, regardless of the histologic subtype. The utility of the Oncotype DX in decision making for treatment of invasive lobular carcinoma (ILC) has not been investigated.

Methods: We performed a retrospective analysis of early stage breast cancer patients treated at Penn State Cancer Institute from 2001 to 2011 and identified 102 patients with ILC. We evaluated the clinicopathological features and compared the Recurrence Score (RS) distribution in this population to that reported by Genomic Health for the ductal histology (Kruskal-Wallis test). Median follow-up was 4.5 years.

Results: We found that the RS distribution for ILC differed significantly from that reported by that reported by Genomic Health (P < 0.0001). The vast majority of patients (97.9%) have low/intermediate RS and only 2.2% high RS whereas the RS distribution reported by Genomic Health is 54.2% for low RS, 20.6% for intermediate and 25.2% high RS. We also found a statistically significant difference in the RS distribution between pure ILC and pleomorphic ILC (P = 0.027). When using RS of 25 as cutoff for chemotherapy recommendation, 93.3% of ILC patients have RS ≤ 25 and would not be candidates for adjuvant chemotherapy. Most tumors were T1-T2 (93.3%) and 6.5% were T3. Most tumors (64.4%) were node negative, 21% had 1-3 lymph nodes positive and 14.4% had N2/N3 disease. All the pure ILC tumors were hormone positive and only one pleomorphic ILC tumor was HR negative. 5.8% tumors were Her 2 +.

Conclusion: The Oncotype DX RS assay in invasive lobular carcinoma is unique, differing significantly from that in invasive ductal carcinoma. Majority of patients (97.9%) have low/intermediate RS and 93.3% have RS ≤ 25 and would not be candidates for adjuvant chemotherapy. The clinical usefulness and cost-effectiveness of the Oncotype DX in guiding treatment for ILC should be further investigated.

Legal entity responsible for the study: Jesse Felts Cristina Truca

Funding: Pink Zone and Lady Lion Basketball Breast Cancer Research Endowment and the Federal US Work Study program

Disclosure: All authors have declared no conflicts of interest.

149PD

Prognostic impact of proliferation for resected early stage breast cancer according to histology: Cut-off analysis of Ki67 in 859 patients with pure invasive lobular and ductal breast cancer (ILC/IDC)

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1Medical Oncology, ADU Integrata Verona “Borgo Ronan”, Verona, Italy.
2Biostatistics Unit, Istituto Regina Elena, Rome, Italy.

Results: We assessed for those who were diagnosed 2004-2011 with survival follow-up through 2012, by RS category and by number of positive nodes.

Results: The proportion of women with LN + , HR + , HER2-negative BC. We assessed 5-year BC-specific survival (BCSS) in LN+ patients with 21-gene RS results in the SEER registries, a cancer surveillance program that covers 30% of the US population.

Background: The 21-gene RS assay has been shown to predict BC recurrence and adjuvant chemotherapy benefit in LN + , HR + , HER2-negative BC. We assessed 5-year BC-specific survival (BCSS) in LN+ patients with 21-gene RS results in the SEER registries, a cancer surveillance program that covers 30% of the US population.

Methods: All SEER BC cases diagnosed 2004-2012 were linked to 21-gene assays in SEER registries. A cancer surveillance program that covers 30% of the US population.

Results: At a median follow-up of 75 months, 10-yr OS and DFS for ILC and IDC were 81.7%/83.4%, and 71.4%/76.2%, respectively. The MSLRS analysis identified 4% and 18% as optimal Ki67 cut-offs for OS for ILC and IDC, respectively. At the multivariate analysis Ki67, Performance Status (PS), nodal status (N), and TNM-tumor-size (T-size) were independent predictors for OS in ILC pts. Ki67 highly correlated at the internal cross-validation analysis. For IDC pts, PS, age, estrogen receptor expression and T-size were independent predictors for OS. With regard to DFS, the MSLRS analysis identified 4% and 14% as optimal Ki67 cut-offs for IDC and ILC, respectively. PS and N were independent predictors for IDC, while PS, age, grading and T-size were predictors for IDC. Log-rank analysis is shown in the table.
CONCLUSIONS: Overall, 5-year BCSS is excellent in patients with RS <18 and few positive nodes and worsens with increasing number of involved lymph nodes and with higher RS. Updated data with longer follow-up is will be presented.

Clinical trial identification: N/A

Legal entity responsible for the study: Dave P. Miller, Megan Roberts, Lynne Penberthy

Funding: National Cancer Institute

Disclosure: D. P. Miller, S. Shak. Employed by Genomic Health; stock ownership in Genomic Health

All other authors have declared no conflicts of interest.

Table 15S5PD

<table>
<thead>
<tr>
<th># of positive LN</th>
<th>N 5-y BCSS (95% CI)</th>
<th>N 5-y BCSS (95% CI)</th>
<th>N 5-y BCSS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micromet only</td>
<td>1</td>
<td>108</td>
<td>99.2 (97.2-99.9)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>300</td>
<td>97.8 (97.2-99.9)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>103</td>
<td>94.7 (77.6-98.9)</td>
</tr>
<tr>
<td></td>
<td>4+</td>
<td>82</td>
<td>85.7 (33.4-97.9)</td>
</tr>
</tbody>
</table>

Prognostic impact of interval breast cancer detection in women with pT1aN0M0 breast cancer with HER2-positive status: results from a multicenter population-based cancer registry study

A. Muscillo1, A. Sikok1, D. Boggi1, A. Rimaini2, B. Pellegrino3, E.M. Sillini3, R. Campari3, E. Barbiere4, L. Cortesi5, M. Parenico5, R. Porzio5, A. Frassoldati1, P. Siangi1, R. Fagini1, M. Michiara1

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Background: Patients (pts) with pT1aN0M0 breast cancers (BCs) have an excellent outcome across all biologic subtypes. HER2 overexpression occurs in 15-20% of primary BCs, and is associated with poor prognosis. Women with BCs diagnosed in the interval between scheduled screening rounds have poorer stage-specific survival than women with screen-detected (SD) tumors, and an association has been reported between interval cancers (ICs) and HER2 overexpression. We aimed to determine, in a general population of pT1aN0M0 BCs with known screening status, if HER2-positive status maintains its negative prognostic value only in tumors diagnosed as ICs.

Methods: All incident pT1aN0M0 BCs (n = 974), systematically collected by the Cancer Registry of Emilia Romagna Region (northern Italy) and diagnosed in women aged 50-69 from 2003 to 2009 were evaluated. Pts unexposed to screening, with unknown HER2 status and/or treated with adjuvant tamoxifen were excluded from analysis.

Results: Twenty percent of BCs were HER2-positive. Fifty-three percent were SD tumors, while 18% were ICs. BCs with high histologic grade (odds ratio [OR] =2.2; 95% CI, 1.1–5.7), hormone receptor negative (OR =2.6; 95% CI, 1.4–4.9), or HER2-positive (OR =2.4; 95% CI, 1.2–5.5) were more likely to be diagnosed as ICs. With a median follow-up of 115 months, the 8-year invasive disease-free survival (IDFS) for ICs was lower than that for SD tumors: 92% (95% CI, 88% to 94%) vs. 97% (95% CI, 95% to 99%; P = 0.011). Notably, HER2-positive ICs showed poorer IDFS than HER2-positive SD tumors (78% vs. 95%, respectively; P = 0.003). An interaction between IC detection and HER2-positive status was found for poorer IDFS after adjusting for prognostic variables (P = 0.007).

Conclusions: In a general population of pT1aN0M0 early BCs with known screening status, IC detection may identify pts with HER2-positive pT1aN0M0 tumors in whom the rate of recurrence justifies consideration for conventional anti-HER2 adjuvant treatment.

Clinical trial identification: N/A

Legal entity responsible for the study: University Hospital of Parma

Funding: “Alessandro Liberati Program” for young investigators; Programma di ricerca Regione Universita 2010–2012 – Regione Emilia-Romagna (Italy)

Disclosure: All authors have declared no conflicts of interest.

A pilot study of neoadjuvant talazoparib for early-stage breast cancer patients with a BRCA mutation


1Breast Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, 2Diagnostic Radiology, MD Anderson Cancer Center, Houston, TX, USA, 3PathoLogicis, MD Anderson Cancer Center, Houston, TX, USA, 4Institute of Biotechnology, MD Anderson Cancer Center, Houston, TX, USA, 5MD Anderson Cancer Center, Houston, TX, USA

Background: Single agent PARP inhibitors have not been evaluated in untreated BRCA mutation carriers with early stage breast cancer. Concerns over efficacy and delay of initiation of chemotherapy may inhibit accrual in the neoadjuvant setting. In this pilot study, we evaluated if patients (pts) would accrue to a non-chemotherapy as their first treatment and if the toxicity profile would be acceptable.

Methods: The study was approved by the Institutional Review Board. Eligibility included ≥ 1 cm tumor and germline BRCA mutation. HER2+ tumors were excluded. Pts underwent a pre-treatment biopsy 2 months of talazoparib monotherapy. The average volume loss was 78% (range 30-98%). Talazoparib was well tolerated with no grade 4 toxicities and only one patient requiring dose reduction due to grade 3 neutropenia. Common toxicities were neutropenia (n = 11), anemia (n = 8), nausea (n = 7), dizziness (n = 8) and fatigue (n = 8), which were grade 1, except: neutropenia (grade 2 = 4; grade 3 = 3) and grade 2 anemia or thrombocytopenia (n = 1 each). To date, pts have had no difficulty with transition to chemotherapy.

Conclusions: Given the profound clinical response with only 2 months of therapy and favorable toxicity profile, this pilot study was discontinued early after 13 pts accrued within 8 months at a single institution and 6 incidences of grade IV toxicity. An expansion cohort to estimate pathologic response to talazoparib alone with 4-6 months is underway.

Clinical trial identification: NCT0228345
Gestational breast cancer: distinctive molecular and clinico-epidemiological features. GEICAM/2012-03 study

Background: Incidence of gestational breast cancer (GBC) (during pregnancy, lactation or first year postpartum) ranges from 6-13% of BC in the 20-44 subgroup age. GBC is associated with positive nodes, negative hormonal receptors (HR), triple negative and high grade tumors but little is known at molecular level. We explore specific genomic and clinico-epidemiological features of GBC.

Methods: Expression of 105 genes was assessed in 50 evaluable tumors from 70 GBC Spanish patients using nCounter platform. The following signatures were assessed: 1) Intrinsic subtypes; 2) Proliferation (P) and Risk of Recurrence (ROR) scores; 3) Claudin-low and 4) Chemo-Endocrine Sensitivity Predictor (CESP). Genomic profile enriched (44% vs 14%, p < 0.01) and Luminal A was less prevalent (14% vs 28%, p = 0.02) in GBC compared to GEICAM/9906 and Málaga combined dataset.

Results: Out of the 70 patients, 43% were diagnosed during pregnancy and 57% postpartum. The table reports patient and tumor characteristics:

<table>
<thead>
<tr>
<th>Feature</th>
<th>GBC</th>
<th>Alamo III</th>
<th>Málaga</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at diagnosis</td>
<td>35</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Negative HR</td>
<td>30 (43)</td>
<td>330 (24)</td>
<td>33 (16)</td>
</tr>
<tr>
<td>T2 T4</td>
<td>51 (76)</td>
<td>787 (56)</td>
<td>176 (60)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>38 (63)</td>
<td>479 (40)</td>
<td>121 (44)</td>
</tr>
<tr>
<td>Ki67 (≥20%)</td>
<td>53 (89)</td>
<td>299 (61)</td>
<td>46 (22)</td>
</tr>
<tr>
<td>Family history of BC</td>
<td>32 (47)</td>
<td>296 (25)</td>
<td>-</td>
</tr>
<tr>
<td>Mean age at first partim</td>
<td>31</td>
<td>26</td>
<td>-</td>
</tr>
</tbody>
</table>

Conclusions: GBC differential biology is suggested by higher Basal-like and lower Luminal A rates, and absence of Claudin-low phenotype, correlating with worse survival and a more aggressive clinico-pathological profile confirmed by a higher ROB-P high rate and lower CESP score.

Changes in breast cancer incidence may be attributed to implementation of all-national dispensationization: a population-based study from North-West Russia

Background: Breast cancer (BC) is the most common cancer pathology among women worldwide and leading cause of death in the developed and less developed countries. Consequently, there were two projects implemented in 2006 (National project “Health”) and in 2013 (Law of All-national dispensationization) focusing on improvement in health care delivery in Russia. The aim of study is to evaluate the effects of the projects on incidence and stage proportion in breast cancer.

Methods: In this retrospective population-based study, we analyzed data from the Arkhangelsk regional Cancer Registry over a period of 15 years (2000-2015). The databases for the analysis included female gender only, date of birth, date of diagnosis, and stage according to the TNM 7 classification. Age-standardized rates per 100,000 person-years were calculated, using the direct method of standardization to the world population. The Joinpoint Regression Analysis program, version 4.2.0.2., was used to calculate trends of BC incidence and Stage proportions.

Results: Over the period of study, 5842 cases of breast cancer were recorded in the Arkhangelsk Regional Cancer Registry. The incidence of breast cancer has been increasing over the period from 35 to 50 cases per 100,000 between 2000 and 2014 with annual percentage change (APC) varying from 0.9% during a period 2000-2006 and 3.9% in 2007-2014. The proportion of Stage 1 variance from 9% to 21% between 2000 and 2014. In Joinpoint regression a significant growth of Stage 1 proportion was observed over the period 2011-2015 with APC 15.7%.

Conclusions: Over the past 15 years there has been a steady increase in breast cancer incidence in the Arkhangelsk region. Taking into account a significant growth of Stage I BC over the latter 4 years, this increase is at least partially explained by better earlier diagnosis after the implementation the All-national dispensationization in Russia. The National project “Health” is less responsible for the increased incidence.

Accuracy and adequacy of pre-operative bracketing for therapeutic excision of non-palpable malignant breast lesions

Background: Brachytherapy comprises of using two or more needles for localization of boundaries of an impalpable breast lesion. The tissue around the wires is excised and sent for histopathology. Objectives: To determine the accuracy & adequacy of pre-operative bracketing for therapeutic excision of non-palpable malignant breast lesions and in achieving tumor free margins.

Methods: Retrospective review of mammograms & pathology reports of patients who underwent bracketing for malignant breast lesions at AKUH from January 2004 to April 2016. All cases of clinically non-palpable primary malignant breast lesions requiring therapeutic excision and with complete clinical response to Neoadjuvant therapy targeted for breast conservation were included whereas those with benign pathology were excluded.

Results: 76 patients with mean age of 48.09 years (range 25 - 81 years) underwent bracketing for excision of both benign and malignant breast lesions. 62 patients underwent breast conservation surgery for a pre-operative diagnosis of IDC (n = 56), ILC (n = 3), DCIS (n = 2) and metaplastic carcinoma (n = 1) with the help of bracketing. 85.9% (n = 53) received neo-adjuvant chemotherapy to reduce the size of lump. 93.5% (n = 58) underwent stereotactic wire localization, 4.8% (n = 3) underwent sonographic localization whereas 1.6% (n = 1) was localized with the help of both mammogram and ultrasound. Presence of radiopaque marker within the excised specimen and grossly adequate margins around the lesion guided the surgeon to decide about further margin excision. 95.2% (n = 59) had negative margins of the breast lump and 2 out of 62 patients, (3.2%) had close margins (DCSS 0.1 cm from closest margin). 1.6% (n = 1) patient had invasive tumor at the margin. None of the re-excised tissue in 2 patients with close margins showed any evidence of tumor in the final histopathology report except the patient with positive margin who underwent second procedure of margin excision followed by mastectomy.
Conclusions: Our study showed that bracketing wire localization is a beneficial procedure in terms of achieving clear histologic margins in breast conservation surgery without significant increase in the rate of re-excision.

Legal entity responsible for the study: The Aga Khan University and Hospital

Funding: The Aga Khan University Hospital

Disclosure: All authors have declared no conflicts of interest.

Ultrasonic-guided core needle biopsy could replace sentinel lymph nodes biopsy for patients with suspicious node positive breast cancer

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Background: The 20011 trial indicated that the information achieved by axillary dissecting lymph nodes (Ax LNs) does not change the prognosis of the disease for patients with clinical node negative breast cancer. Several clinical trials conducted the need for SNB in cases with negative ultrasound-guided (US) fine needle aspiration cytology (FNA) of the suspicious LNs. The aim of this study was to evaluate the reliability of CNB to detect positive LN compared to that of FNA.

Methods: A total of 1465 consecutive patients (pts) with breast cancer were prospectively identified at our institution between March, 2012 and 2016. The inclusion criteria of both FNA(21G) and CNB(16G) was cortical thickness greater than 3 mm or abnormal morphologic characteristics. Patients with biopsy-proved metastases underwent Ax, and those with a negative FNA or CNB underwent SNB. If the SNB was positive, Ax was performed. Diagnostic accuracy was calculated for FNA and CNB.

Results: The number of negative US of LNs was 744 pts, 440 FNA and 212 CNB were performed for suspicious LNs. Sensitivity, specificity, PPV, NPV, and accuracy were 83%, 99%, 97%, 88%, and 91% in FNA, and 93%, 99%, 97% and 97% in CNB, respectively. SNB was performed in 141 of 212 CNB and 254 of 463 FNA. 141CNB (T1:83,T2:52,T3:9 pts) treated with SNB were compared to 254 FNA (T1:127,T2:116,T3:11 pts) regarding the number of LNs metastasis. The number of positive SLNs and positive LNs more than 3 was 5 (4%), 0(0%) in CNB, and 35(14%), 15(6%) in FNA, respectively.

Conclusions: CNB is a reliable method for the preoperative diagnosis of LNs metastasis. If CNB shows negative LNs, SNB might be safely omitted for patients with breast cancer.

Clinical trial identification: none

Legal entity responsible for the study: N/A

Disclosure: All authors have declared no conflicts of interest.

Endoscopy-assisted breast surgery for breast cancer: updated results from study conducted by the Taiwan Endoscopic Breast Surgery Cooperative Group

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Background: Endoscopic-assisted breast surgery (EABS) performed through minimal axillary and/or peri-areolar incisions is a possible alternative to open surgery for certain patients with breast cancer. In this study, we report the early results of an EABS program in Taiwan.

Methods: The medical records of patients who underwent EABS for breast cancer during the period May 2009 to December 2015 were collected from the Taiwan Endoscopic Breast Surgery Cooperative Group database. Data on clinicopathologic characteristics, type of surgery, method of breast reconstruction, complications and recurrence were analyzed to determine the effectiveness and oncologic safety of EABS.

Results: A total of 345 EABS procedures were performed in 320 patients with breast cancer, including 25 (7.2%) patients with bilateral disease. The number of breast cancer patients who underwent EABS increased initially from 2009 to 2012 and then stabilized during the period 2012–2015. The most commonly performed EABS was endoscopy-assisted total mastectomy (EATM) (85.8%) followed by endoscopy-assisted partial mastectomy (EAPM) (14.2%). Approximately 76% of the EATM procedures involved breast reconstruction, with the most common types of construction being implant insertion and autologous pedicled TRAM flap surgery. During the seven-year study period, there was an increasing trend in the performance of EABS for the management of breast cancer when total mastectomy was indicated. The positive surgical margin rate was 1.4%. Overall, the rate of complications associated with EABS was 13.2% and all were minor and wound related. During a median follow-up of 31.7 (4.2–75.6) months, there were 3 (1%) cases of local recurrence, 5 (1.4%) case of distant metastasis and 2 (0.5%) death.

Conclusions: The updated results from the EABS program in Taiwan show that EABS is a safe procedure and results in acceptable cosmetic outcome. These findings could provide an alternative in surgical technique for certain breast cancer patients.

Clinical trial identification: IRB No.: 141224

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Disclosure: All authors have declared no conflicts of interest.

The role of preoperative breast magnetic resonance (MR) imaging for surgical decision in patients with triple-negative breast cancer


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Background: Several reliable randomized studies do not recommend routine preoperative breast MR imaging for patients with breast cancer. However, because the principle of MR imaging is based on the dynamics of contrast enhancement, a specific biologic subgroup of tumors should sensitively respond to the imaging process.

Methods: From 2008 to 2013, 918 eligible patients with breast cancer underwent breast surgery and were divided into two groups based on preoperative breast MR findings. Patients in whom the surgical plan was changed and those in whom the surgical plan remained unchanged. We investigated the changing patterns of breast surgery based on routine mammography, ultrasound, and preoperative breast MR findings and analyzed the association between additional suspicious lesions on breast MR imaging and clinicopathologic factors.

Results: Additional suspicious breast lesions were detected on preoperative MR imaging in 104 cases (11.3%), and the surgical strategy was changed as the final decision in 97 cases (10.6%). There was no difference between oncologic results between two groups. However, the triple-negative breast cancer (TNBC) was significantly associated with changing of the surgical strategy based on breast MR findings (P = 0.048).

Conclusions: Additional preoperative breast MR imaging may be helpful in surgical decision for patients with TNBC.

Legal entity responsible for the study: Department of Surgery, Kyungpook National University School of Medicine

Funding: Department of Surgery, Kyungpook National University School of Medicine

Disclosure: All authors have declared no conflicts of interest.

What decides breast conservation versus mastectomy in the background of diverse sociocultural environment, an Indian study

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Background: Breast cancer is the most common cancer in Indian females, about a third being operable. The reason for low rates of BCS in early breast cancer (EBC) is multifactorial inspite of results from SABCS 2015 which revealed better survival in BCS patients than in mastectomy group. India is a culturally rich, multilingual and diverse nation, with many communities which live in their respective social structures, contributing to low rates of BCS. Understanding these multidimensional psychosocial, and cultural factors are essential for providing comprehensive and appropriate cancer care. Our objective was to look at factors that influence the type of surgery in EBC in our diverse cultural and socioeconomic background and to improvise.

Methods: 153 EBC patients at Apollo hospitals from Jan 2014 to June 2015, were interviewed regarding various factors which influence the surgical decision. The questionnaire included literacy, economic status, single or joint family, rural or urban, deciding factor- patient preference, family and surgeon, psychological impact in terms of anxiety or depression and fear of tumour recurrence.

Results: Of the total 153 EBC patients, 56 (36%) had BCS and rest (90) 64% had MRM. BCS group had more urban population (64 %) than in mastectomy group (56%). BCS group had higher education level (66% graduates) as opposed to patients undergoing MRM (23% graduates). Higher proportions of younger women was observed in the BCS (69% group as opposed to total mastectomy group (33%). Surgeon seemed to play a major role in making MRM decision (67%) as compared to BCS (11%) in contrast to western scenario where patient has a major role in decision making. BCS group had significant patient involvement (39%) in decision making as compared to 10% in MRM group.

Conclusions: Various reasons such as patient identification, surgeon’s role and economic status are factors that influence the choice of surgical decision in patients with breast cancer. Understanding these factors will help the surgeons improvise their surgical technique, as per the sociocultural background of the patients.
Menopausal status on tumour biology in early breast cancer

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Background: Breast cancer (BC) is primarily a disease of older or post menopausal women. It has been suggested that BC arising in young women is a unique biological subset characterized by less hormone sensitivity and higher HER2 (epidermal growth factor) receptor expression. This study was performed to compare the tumour biology between pre menopausal (PrM) and post menopausal (PoM) women.

Methods: New diagnosis of early BC from 2011-2015 in the South East Access Centre were included. The patients were divided into PrM (<55 years) and PoM (≥55 years) groups. Information on pathology subtype (ductal carcinoma/infiltrating carcinoma), tumour grade, T-stage, N-stage (N), and anatomical stage was obtained. Comparisons between these factors in the two groups were drawn using SPSS version 20.0.

Results: Data from 497 patients were obtained: 235 (47.3%) were PrM and 262 (52.7%) were PoM. Age range PrM group vs PoM group (29-54 vs 55-91). The differences between the groups were statistically significant on pathology subtype (p < 0.003), T-stage (p = 0.038), and N-stage (p = 0.008). Ki67 and grade were not statistically significant. The mean ki67 across biology subtypes (ER/PR/HER2/Ki67) in the PrM group was higher. PrM group had more grade III disease (33.2% vs 30.9%). Table 1: Distribution of tumour biology according to menopausal status.

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Pathology ICD LCC</th>
<th>T stage</th>
<th>Ki67 (%)</th>
<th>N stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 255</td>
<td>214 23 204 53</td>
<td>2 3 4</td>
<td>0.21 0.39</td>
<td>0.008</td>
</tr>
<tr>
<td>n = 262</td>
<td>17 48 27 2</td>
<td>0.034</td>
<td>0.083</td>
<td>0.033</td>
</tr>
</tbody>
</table>

*mean, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma.

Conclusions: Pre menopausal women in this Irish population had poorer tumour biology compared to their Post menopausal counterpart. Aggressive measures should be taken in the treatment of these women to reduce the incidence of local recurrence and metastases.

Legal entity responsible for the study: University Hospital Waterford

Funding: University Hospital Waterford

Disclosure: All authors have declared no conflicts of interest.

Breast cancer Ki67, tumor size and axillary nodes relationship: It’s complicated

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Background: The cell proliferation labeling index Ki67 is a discussed parameter for treatment decision in breast cancer (BC). Prior works have not settled the question whether Ki67 is independent of other tumor factors. Herein, we investigated the relationship between Ki67, tumor size (T-size) and age with axillary lymph node metastases (ALNM) in early BC patients (pts).

Methods: We analyzed 1,785 pts treated for T1-T2 N0-N1 BC from 01/11/2011 to 30/09/2015 at Istituto Nazionale dei Tumori in Milan. Correlation between Ki67 and T-size was calculated by Spearman’s coefficient, p. Associations of ALNM with Ki67 and other tumor characteristics were investigated by logistic regression. Fully adjusted odds ratio (OR) with 95% confidence intervals (CI) were estimated in all cases, and separately analyzed according to T-size and age.

Results: Higher T-size was associated with higher Ki67 values in pts ≥20 years (yrs) (p = 0.348, p < 0.001) with no substantial differences according to hormone receptor (HR) and HER2 status. Such correlation was weaker (p = 0.248, p < 0.001) in pts <50 yrs with HER2 negative BC and absent among HER2 positive BCs. Ki67 values ≥20% were associated with increased odds of ALNM in pts aged ≥50 with T-size ≥10 mm (OR 2.87, 95% CI 1.39-5.92). No relationship was found between Ki67 and ALNM in tumors > 10 mm and in pts aged < 50. The odds of ALNM increased according to T-size (OR for each 5 mm increase 1.42; 95% CI 1.30-1.54) in all BCs except the triple negative (TN). Noteworthy, compared to HR positive HER2 negative tumors, TN cases showed significantly lower odds of ALNM (OR 0.44, 95% CI 0.21-0.91) in T-size >10 to 20 mm and in T-size >20 to 50 mm (OR 0.32, 95% CI 0.16-0.67).

Conclusions: Our analysis seems to exclude significant relation between Ki67 and ALNM, while T-size and ALNM were confirmed to be highly related in all BCs but TN. Given these data it is appropriate to discuss if axillary surgery may be redundant in cases with exceptionally good prognosis and in pts with poor prognosis that will be offered systemic therapy and radiotherapy anyway. Hence BC pts aged > 50 with small tumors and low Ki67 and most TN pts represent ideal candidates for current clinical trials evaluating the potential for eliminating axillary surgery and sentinel node biopsy.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Funding: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Disclosure: All authors have declared no conflicts of interest.

The prognostic performance of Adjuvant! Online and Nottingham Prognostic Index in young breast cancer patients: a multi-centre hospital-based retrospective cohort study

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Background: Adjuvant! Online (AOI) and Nottingham Prognostic Index (NPI) are prognostic tools that are widely used to aid treatment decision-making. Although performing globally well, their performance is unclear in populations other than those used in their validation studies and particularly in specific subgroups such as women ≤40 years. The present study aimed to evaluate for the first time the prognostic performance of AOI and NPI in young breast cancer patients.

Methods: This is a multicentre hospital-based retrospective cohort study including young (≤40 years) and older (55-60 years) breast cancer patients treated from January 2000 until December 2004 at 4 large Belgian and Italian institutions. Predicted 10-year overall survival (OS) and disease-free survival (DFS) using AOI and 10-year OS using NPI were calculated for every patient. To assess calibration, the trimmed mean of the predicted 10-year outcomes was compared to the observed (Kaplan-Meier estimate at 10 years) by using one-sample t-test. Discriminatory accuracy was assessed by calculating the area under the receiver-operator characteristic curve and the corresponding 95% confidence intervals for 10-year predicted OS and DFS. Vital status was cross-checked with the national registries in Belgium and Italy.

Results: A total of 1,283 patients were included (376 in the young and 907 in the older cohorts, respectively). AOI accurately predicted 10-year OS (absolute difference: 0.66%; p = 0.37) in the young cohort, but overestimated 10-year DFS by 7.66% (p = 0.003). In the older cohort, AOI significantly underestimated both 10-year OS and DFS by 7.29% (p < 0.001) and 3.12% (p = 0.04), respectively. NPI significantly underestimated 10-year OS in both the young (8.46%; p < 0.001) and the older (4.04%; p < 0.001) cohorts. AOI and NPI had comparable discriminatory accuracy in predicting both OS and DFS.

Conclusions: In young breast cancer patients, AOI is a reliable tool in predicting OS at 10 years but not DFS, while the calibration performance of NPI is suboptimal. In patients aged 55-60 years, the role of AOI and NPI deserves further investigations.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
Tumor lymphocyte infiltrations decrease the risk of late relapse in breast cancer patients

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Background: Tumor lymphocyte infiltrations (TLI) seem to be a prognostic factor for survival in hormone receptor negative breast cancer (i.e. triple negative and HER2 positive). The majority of breast cancer patients relapse early in the first five years after diagnosis. The impact of TLI on late relapses in breast cancer patients is unknown.

Methods: Data of patients with early breast cancer treated in years 1984-1988 at the Institute of Oncology Ljubljana, Slovenia, were analysed retrospectively from patient’s charts. We evaluated the prognostic value of TLI on late relapses (>5 years after diagnosis).

Results: In 1034 patients (median age 57 years, 61% postmenopausal) primary treatment was surgical by modified radical mastectomy (87%) or breast conserving surgery (13%). All had axillary dissection and 12% adjuvant radiation. 47% were node negative, 51% size of tumor 2-5 cm, 40% grade II and 21% grade III, 15% had lymphovascular invasion (LVI) and 42% TLI. 50% positive estrogen receptors (ER), 30% positive progesterone receptors (PR). HER2 status was unknown. 30% of patients received adjuvant chemotherapy (CMF schedule), 16% adjuvant hormonal therapy with tamoxifen, and 3% both chemo- and hormonal therapy. 516 (39%) of patients relapsed during the whole follow up time (median follow up time was 26.5 years). At 5 years 595 patients were alive and relapse-free, 150 (14.5%) patients relapsed after 5 years after diagnosis. In univariate analysis TLI (HR 0.56; 95% CI 0.40-0.78), nodal stage (HR 1.39; 95% CI 1.14-1.69) and PR (HR 1.78; 95% CI 1.25-2.54) were found as prognostic factors for relapse. ER (HR 1.39; 95% CI 0.99-1.95) and LVI (HR 1.63; 95% CI 0.97-2.73) were nearly statistically significant. In multivariate Cox analysis a favourable prognostic factor for relapse was TLI (HR 0.58; 95% CI 0.40-0.84, p = 0.004) and two unfavourable prognostic factors were positive PR (HR 1.65; 95% CI 1.14-2.39, p = 0.007) and nodal stage (HR 1.43; 95% CI 1.13-1.86, p = 0.03).

Conclusions: Our data indicate that TLI could decrease the risk of late relapse in breast cancer patients indicating the significance of immune response mechanisms as a potential therapeutic target in breast cancer. Prospective studies to test this hypothesis are needed.

Clinical trial identification: National Medical Ethics Committee at Ministry of Health, Republic of Slovenia, Number 121/07/02

Legal entity responsible for the study: Institutional ethics committee, Institutional review board

Funding: None

Disclosure: All authors have declared no conflicts of interest.

The let-7/Lin28 can be an early detection marker of anti-HER2 containing therapy sensitivity in HER2 positive breast cancer

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Background: Anti-Human epidermal growth factor receptor (HER) 2 therapy, trastuzumab for HER2 positive breast cancer patients improved their prognoses dramatically. However, there are some potentially trastuzumab-resistant breast cancer even in trastuzumab-naive patients. Therefore, understanding of the molecular mechanism of trastuzumab resistance is strongly demanded. In this study, we hypothesized that micro RNA (miRNA) play important roles in trastuzumab treatment.

Methods: We performed comprehensive microRNA expression profiling of pre-treatment biopsy specimens in 83 HER2 positive breast cancer patients who underwent preoperative trastuzumab-chemo combined therapy. Then, let-7 family expression in cancer cells was elevated in non-pCR cases compared to pCR cases. Thus, we tried to elucidate molecular mechanisms associated with trastuzumab sensitivity and let-7 expression. We investigated their function in HER2 positive human breast cancer cell lines, trastuzumab-sensitive and -resistant. These two cell lines were used for gain/loss of function experiments. We also attempted to prove their correlations between let-7 family expression and clinical outcome.

Results: The expression of let-7 family is regulated by LIN28 because it forms a double negative feedback loop with let-7. Let-7/LIN28 expression was down/up-regulated in BT474 (sensitive) and cells exposed to trastuzumab exposure, respectively, whereas the let-7/LIN28 expression was up/down-regulated in JMET-1 (resistant) cells. Exogenous overexpression of let-7 in BT474 cell decreased trastuzumab sensitivity from 50% to 40% -6 day exposure of trastuzumab. Conversely, let-7 down-regulated JMET-1 cells had down-regulated expression of let-7 family and recovered trastuzumab sensitivity from 0% to 20% (>2ug/mL).

Conclusions: The let-7/LIN28 regulatory circuit may have an important role in molecular mechanisms of trastuzumab-chemo therapy for HER2 positive breast cancer. Early assessment of this let-7/LIN28 response after treatment start might predict treatment outcome. We believe that modulation of this regulatory circuit might sensitize trastuzumab-resistant breast cancer cells.

Legal entity responsible for the study: N/A

Funding: Chugai, Scientific research grant

Disclosure: M. Toi. Chugai Scientific research grant

Other authors have declared no conflicts of interest.

Clinicopathological characteristics and BRCA1/2 mutation rate in male breast cancer: a retrospective case series by the Hellenic Society of Medical Oncology

Male Breast Cancer Working Group, Hellenic Society of Medical Oncology, Athens, Greece

Background: Due to its rarity, male breast cancer (MBC) remains an inadequately characterized disease. Germline mutations in the BRCA1/2 genes are considered the most significant risk factor for MBC development.

Methods: We retrospectively analyzed the clinicopathological characteristics, treatment patterns, and the BRCA1/2 germline mutation rate of BC patients (pts) treated from 1995 to 2014. Pts who were still alive were identified and were invited for genetic counseling and testing. The study was coordinated by the University of Crete School of Medicine.

Results: A total of 166 pts were identified through their medical records. Median age at diagnosis was 64. Family history of either FBC or ovarian cancer was positive in 19.9% while 4% had a personal history of gynecostasia. Histology was of Ductal Invasive type in 84% of the pts. Node positive locally advanced disease was diagnosed at 30% of pts, while 18% were metastatic at presentation. ER and/or PR positive, HER2-negative was the predominant subtype (78.4%), followed by triple-positive (18.1%) and only in few pts triple-negative subtype (3%). Histologic grade distribution was gr. I in 5.4%, gr. II in 53.4% and gr III in 41%. All 99 pts who received genetic counselling consented to BRCA1/2 genetic testing. Overall BRCA1/2 deleterious mutation rate was 6% (5% BRCA2 and 1% BRCA1), while 3 pts (3%) carried a VUS. Most pts (80%) underwent modified radical mastectomy, 41% of which received adjuvant radiotherapy. Adjuvant systemic therapy was administered to 71.6% (10% had chemotherapy only, 27% hormone therapy only and 63% both). Metastatic disease was treated with at least 1 line of systemic therapy in 31.9% of pts (chemotherapy in 60% of them), 60% of which proceeded to subsequent lines.

Conclusions: In one of the largest national cohorts of MBC pts reported yet, we confirmed similar biological patterns to post-menopausal FBC. BRCA1/2 germline mutation rate is comparable to other European populations. Male Breast Cancer Working Group of the Hellenic Society of Medical Oncology Koumarianou A., Bournaakis E., Boutis A., Diamantopoulos N., Katsoounis P., Korantzas I., Lianos E., Tsokulas N., Bakorgeorgos M., Kalampaki T.

Legal entity responsible for the study: N/A

Funding: NSRF (National Strategic Reference Framework), Hellenic Ministry for Health and Social Solidarity

Disclosure: All authors have declared no conflicts of interest.

Triple-negative breast cancer and BRCA mutation: looking at the future

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Background: More than 75% of breast carcinomas that develop in BRCA mutation carriers (BRCA+ are triple-negative breast cancer (TNBC). Despite higher prevalence, it is controversial whether BRCA+ have lower survival. The aim of this study was to compare disease free survival (DFS) and overall survival (OS) in TNBC patients with and without deleterious BRCA1/2 mutations.

Methods: A total of 116 women with TNBC referred to our Institution for genetic counseling and underwent BRCA genetic testing between 2002 and 2015, 13 patients with a BRCA variant of uncertain significance (VUS) were excluded. Associations between clinical features and outcomes were evaluated using univariate and multivariate Cox analysis.

Results: Overall, 103 women were included, 55 (47%) were BRCA+ (BRCA1 n = 48, BRCA2 n = 7) and 48 cases wild-type (BRCA-). Recurrent mutations were: 2 framework mutations in exon 11 in 5 cases with 3901delT and 4 with 962delE Stop 297 respectively. Six patients presented exon 5 framework mutation (380T>G) and 5 women presented large genomic rearrangement (Del 1 and 2). Median age was 42 years in BRCA+ and 48 years in BRCA-. The two patient groups were comparable for prognostic factors. Median follow-up was 6.2 years (range 0.5-22.8), the 5-year RFS rates were 79% and 72% (P = 0.12) in BRCA+ and BRCA- and 5-year OS rates was 83% in both groups. No significant prognostic difference was evidenced in DFS (p = 0.54)
Annals of Oncology


BRCa mutations and IGF-R1 expression in modulating sensitivity to trastuzumab in HER2-positive breast cancer

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Methods: We analyzed data from 35 patients treated with adjuvant/neoadjuvant Trastuzumab and/or after development of metastasis (17.1%). We performed immunohistochemistry for HER2, ER/PR, Ki67 and IGF-R1. Bioinformatic analysis was carried out to identify any correlation among HERE overexpression, BRCa mutations and IGF-R1 expression.

Results: Three previously reported BRCa1 pathogenic mutations, c.5161C>T, c.5382insC, and c.300T>G and one BRCa2 pathogenic mutation c.466dup were observed in 4 patients (16.7%). Additionally, novel variant BRCa2 c.7544C>T was predicted to be pathogenic in silico. Only two of the observed mutations is included in routine BRCa testing in Russia (18FdA405, 413dA405, 5835insC, 3919dG7TAA, 887RdGCTG, 309T>G (c.6174G7R) and usage of standard real-time PCR kits would cause false negative results.

Conclusions: The study demonstrated that breast cancer individuals in Tatar ethnic possess different founder mutation in BRCa genes. Thus, current genetic testing protocol for Russian BRCa1 founder mutation is not enough sensitive for clinical use and nationalization to has been taken into account.

Legal entity responsible for the study: N/A

Funding: Kazan (Volga Region) Federal university Kazan Clinical Oncology Center Federal Research and Clinical Center, FMBA

Disclosure: All authors have declared no conflicts of interest.

Transcriptomic stratification of breast carcinomas with double-equivocal HER2 status

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Background: The evaluation of HER2 overexpression and amplification in breast cancer (BC) provides a validated predictor of response to anti-HER2 agents. However, the algorithm based on immunohistochemistry (IHC) and in situ hybridization (ISH) still identifies a category of carcinomas (double equivocal) that remain equivocal after ISH testing ("double equivocal" carcinomas). These carcinomas represent a real challenge for oncologists, who have to face the dilemma "to treat or not to treat".

Methods: We retrieved a series of 28 formalin fixed paraffin embedded double equivocal BCs using transcriptomics.

Results: All cases were estrogen receptor positive and 68% showed progesterone receptor expression in more than 20% of tumor cells. The large majority of double equivocal BCs were classified as Luminal B molecular subgroup (23/28, 82%), three cases (11%) were predicted to be pathogenic in silico. Only two of the observed mutations is included in routine genetic testing protocol for Russian BRCa1 founder mutation is not enough sensitive for clinical use and nationalization to has been taken into account.

Conclusions: Double equivocal BCs preferentially pertain to the Luminal B rather than to the HER2-enriched molecular subgroup. Nevertheless, our data show that these luminal carcinomas, even when node negative and of small tumor size, preferentially harbor a high risk of recurrence. This transcriptomic stratification may help in the treatment decision making of this controversial category of BC.

Legal entity responsible for the study: University of Turin

Funding: Italian Association for Cancer Research

Disclosure: All authors have declared no conflicts of interest.

Screening for caspase activity combined with the ratio of T-cell subsets in the peripheral blood as potential diagnostic tool in breast cancer

U.S. Bagina1, L.V. Shchegoleva2, T.O. Volkova2

Background: In the personalized medicine era, there is essential demand of creating a universal user-friendly as well as cost-effective detection test-system for breast cancer, which assigns the molecular subgroup and provides a prediction of risk of recurrence in breast cancer patients.

Methods: We developed a colorimetric test for detecting caspase-3 activity as a marker of tumor necrosis, combined with the ratio T helper/ cytotoxic T cell in breast cancer patients who underwent neoadjuvant systemic treatment (NSTEM). Caspase-3 activity in peripheral blood mononuclear cells (PBMC) was analyzed using the Colorimetric Caspase-3/7 Assay Kit (Biovision). Two-color flow cytometry analysis of T helper and cytotoxic T cell subsets was performed using BV587 conjugated anti-CD4 and PerCP/Cy5.5 conjugated anti-CD8 antibodies (eBioscience). The study included 20 breast cancer patients who underwent cycles of neoadjuvant chemotherapy/ endocrine therapy as part of the primary treatment. The endpoint of the study was a combination of caspase activity in PBMC with T helper/cytotoxic T cell ratio.

Results: A significant decrease of caspase activity and an increase of the T helper/cytotoxic T cell ratio was observed in patients with complete clinical regression, which is a common indicator of biological response to therapy. The results of the study suggest that the combination of caspase activity in PBMC with T helper/cytotoxic T cell ratio may be used as a potential diagnostic tool for evaluating the response to neoadjuvant systemic therapy in breast cancer patients.

Conclusions: Further studies are required to evaluate the clinical utility of this approach in the management of breast cancer patients.
the most prevalent cancer in female population, which would combine non-invasiveness with high-precision performance. Since mammary glands do not produce any specific molecular markers, we studied several molecular biomarkers that are involved in immunoregulation. One of such molecules are caspases, a family of intracellular enzymes that can play protective role in tumorigenesis by inducing apoptotic cell death in lymphocytes.

Methods: Activity of caspases-3, -6, -8, and -9 was assessed in the peripheral blood lymphocytes in patients at different breast cancer stage of breast benign disease (BRBD) and healthy controls. The caspase activity was measured using fluorogenic substrate while cellular apoptosis was evaluated by means of cytofluorometric assay. In addition, the ratio of T-cell subsets was compared using antibodies to CD3, CD4, CD8, CD16, CD20, CD25, CD95 antigens. Discriminant function analysis and artificial neural networks (ANNs) method were used to create test-system.

Results: We obtained statistically significant data in all groups of 138 analyzed samples. Discriminants have revealed significance for all 11 biomarkers. Using the biomarkers, we were able to differentiate correctly 100% of cases without pathology, 87% – BRBD, 1 breast cancer stage – 90%, II stage – 100% and III stage – 100%. By introducing permutation in expanded to 3464 samples size, we were able to increase the sensitivity of the test system that is 100% control samples, 97% – BRBD, 92% - stage I of breast cancer, 99% - stage II, 100% stage III. On the basis of ANNs analysis software was developed in R-statistics. Network produced 100% correct result both on the original selection and on the artificially increased.

Conclusions: Studies have shown that combining of biomarkers with the used algorithms can be successfully used to differentiate pathological blood from controls, classify breast cancer by the stage and separate benign and malignancy breast tumors. Further, the diagnostic system must be blindly tested with new clinical data.

Legal entity responsible for the study: Petrovskod State University


Disclosure: All authors have declared no conflicts of interest.

Expression of androgen receptors in primary breast cancer

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Background: The objective of the study was to evaluate the prognostic effect of androgen receptor (AR) in breast cancers.

Methods: We investigated immunohistochemical AR expression from paraffin blocks of one hundred patients between 2007 and 2011, and analyzed demographics and outcomes using univariate analyses. Tumors with ≥20% nuclear-stained cells were considered positive for AR.

Results: AR was expressed in 62% of patients. AR was significantly related to older age at diagnosis, smaller tumor size, histological type, higher positivity of hormone receptors and the administration of systemic treatment. In estrogen receptor (ER)-negative tumors, AR was distinctively associated with histological type and progesterone receptors unexpression. With a mean follow-up of 35.72 months, AR expression was a significant prognostic factor for DFS and OS in all patients. The 3-year DFS and OS of patients with AR-positive tumor were 87.1% and 90.73%, respectively. The 3-year DFS and OS of those with AR-negative tumor were 66.32% and 84.21%, respectively. AR expression was positively associated with survival outcomes in all patients.

Conclusions: AR is significantly associated with favorable features in breast cancers and related to better outcomes in ER-positive not in ER-negative tumors. These results suggest that AR could be an additional marker for endocrine responsiveness in ER-positive tumors and a candidate for therapeutic targeting of ER-negative tumors.

Legal entity responsible for the study: Tanta University

Funding: Tanta Faculty of Medicine

Disclosure: All authors have declared no conflicts of interest.

Immunohistochemical status of p53 as prognostic factor in patients with node negative triple-negative breast cancer

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Background: TP53 mutations are the most common genomic alteration in TNBC, translation of p53 into the clinical setting is particularly pertinent in TNBC, with p53 mutations reported in over 60-80% of TNBC or BRBCs compared with only 13-26% of luminal breast cancers. However, despite the high incidence of genetic alterations in breast cancer, there is no consensus about the clinical application of p53 to management breast cancer.

Methods: We retrospectively reviewed the clinicopathological records of patients diagnosed with surgically treated invasive breast cancer at Samsung Medical Center between Jan. 2003 and Apr. 2013. During these periods, 7739 patients with complete pathologic data, including tumor size, nuclear grade, multiple tumors, the presence of lymphovascular invasion (LVI), TNM stage, and the expression of estrogen receptor (ER), progesterone receptor (PR) and HER2, Ki-67 and p53 were included in the analysis.

Results: Median follow-up duration of patients was 57 months (4-140 months). Median age of patients was 48 years (21-78 years). Total 1129 patients, 732 patients (64.8%) had no LN metastasis and 397 patients had LN metastasis. In TNBC patients without LN metastasis, p53+ tumors had shown higher nuclear grade than p53- tumors (87.2% vs.81.5%, P = 0.034). And, p53+ tumors had shown higher 21GQ expression than p53- tumors (90.7% vs. 84.8%, P = 0.039). With multivariate analysis, p53 expression (p53+) had shown significantly better OS than patients without p53 expression (p53-) (p53+ VS. p53–, HR 2.8, 95% confidence interval: 1.1-7.1, P = 0.022). However, in patients with LN metastasis, p53+ expression was not associated with DFS. However, in TNBC patients with LN metastasis, there was no difference of clinicopathologic characteristics between p53+ tumors and p53- tumors. And, there was no association with survival, neither DFS nor OS.

Conclusions: Conclusively, in TNBC, p53 expression was associated with better OS in patients with node-negative, not in patients with node-metastasis. These results suggest that p53 expression could be a favorable prognostic factor in early TNBC.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
more so for patients enrolled at hub centers, decreasing the use of CT from 38% to 28% of patients.

Legal entity responsible for the study: Istituto Oncologico Veneto IRCCS

Funding: The sponsor of the study is the Istituto Oncologico Veneto IRCCS in Padua. The study was selected in the contest of the Region Veneto called “Chiamate - nell’ambito di collaborazioni pubblico-private” - alla presentazione di progetti di ricerca, innovazione e formazione in sanit. Anno 2013". A research grant by Genomic Health supported in part the study.

Disclosure: M.V. Ducci: Consulting activity (Genomic Health). P.F. Conte: Research grant (Genomic Health). All other authors have declared no conflicts of interest.
prognostic and predictive factors (age, TNM status, Scarff-Bloom-Richardson grade, inflammatory feature, estrogen receptor status, progesterone receptor status, HER2 status) and did not correlate with breast cancer subtypes. 94-SPN risk score did not predict outcomes represented by overall survival and disease free survival.

**Conclusions:** In a prospective cohort of 8703 patients, a risk score based on 94 SNPs was not associated with breast cancer characteristics, cancer subtypes or patient’s outcomes. If we hypothesize that prognosis and subtypes of breast cancer are determined by constitutive genetic factors, variants associated with breast cancer subtypes and prognosis should be different from variants involved in the risk of developing a breast cancer.

**Clinical trial identification:** SIGNAL / PHARE (NCT00318919 – REC1098).

**Legal entity responsible for the study:** Xavier Pivott - Institut National du Cancer - France

**Funding:** INCa

**Disclosure:** X. Pivott: XP received honorarium from Roche, Eisai. All other authors have declared no conflicts of interest.

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**Background:** The aims of this preliminary study were to evaluate the association between the Oncotype DX (O DX) recurrence scores and traditional prognostic factors and to develop a nomogram that predict a subgroup of patients with low ODX recurrence score (<25), in whom addition of chemotherapy can be avoided.

**Methods:** Clinicopathological and immunohistochemical variables from a series of 396 T1-3N0-1miM0 hormone receptor-positive, human epidermal growth factor-2 (HER2)-negative breast cancer patients with available ODX test results at Asian Medical Center from 2010 to 2015 were retrospectively retrieved and analyzed. One hundred eight (27%) had positive axillary lymph node micrometastases, and 333 (84%) had ODX recurrence scores of ≤25. Logistic regression was performed to build a nomogram for predicting a low-risk subgroup of the ODX assay. The cutoff value of ODX recurrence scores for the low-risk subgroup was set at ≤ 25, which is used in the ongoing Oncotype DX phase 3 TAILORx trial.

**Results:** Multivariable analysis revealed that estrogen receptor (ER) score, progesterone receptor (PR) score, lymphovascular invasion (LVI), nuclear grade, and Ki-67 had statistically significant association with the low-risk subgroup (all p values < 0.001). With these variables, we developed a nomogram to predict the low-risk subgroup with the ODX recurrence scores of ≤25. The area under the ROC curve was 0.90 (95% CI, 0.85-0.96).

**Conclusions:** Low ODX recurrence score subgroup can be predicted by a nomogram incorporating five traditional prognostic factors: ER, PR, LVI, nuclear grade, and Ki-67. An independent prospective validation for the present nomogram is underway to confirm its accuracy.

**Legal entity responsible for the study:** Saebyul Lee

**Funding:** Asian Medical Center

**Disclosure:** All authors have declared no conflicts of interest.

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**Abstract:**

A nomogram for predicting the Oncotype DX recurrence score in women with T1-3N0-1miM0 hormone receptor-positive, human epidermal growth factor-2 (HER2)-negative breast cancer

**S. Lee**

**Surgery, Asian Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea**

**Background:** The aims of this preliminary study were to evaluate the association between the Oncotype DX (O DX) recurrence scores and traditional prognostic factors and to develop a nomogram that predict a subgroup of patients with low ODX recurrence score (<25), in whom addition of chemotherapy can be avoided.

**Methods:** Clinicopathological and immunohistochemical variables from a series of 396 T1-3N0-1miM0 hormone receptor-positive, human epidermal growth factor-2 (HER2)-negative breast cancer patients with available ODX test results at Asian Medical Center from 2010 to 2015 were retrospectively retrieved and analyzed. One hundred eight (27%) had positive axillary lymph node micrometastases, and 333 (84%) had ODX recurrence scores of ≤25. Logistic regression was performed to build a nomogram for predicting a low-risk subgroup of the ODX assay. The cutoff value of ODX recurrence scores for the low-risk subgroup was set at ≤ 25, which is used in the ongoing Oncotype DX phase 3 TAILORx trial.

**Results:** Multivariable analysis revealed that estrogen receptor (ER) score, progesterone receptor (PR) score, lymphovascular invasion (LVI), nuclear grade, and Ki-67 had statistically significant association with the low-risk subgroup (all p values < 0.001). With these variables, we developed a nomogram to predict the low-risk subgroup with the ODX recurrence scores of ≤25. The area under the ROC curve was 0.90 (95% CI, 0.85-0.96).

**Conclusions:** Low ODX recurrence score subgroup can be predicted by a nomogram incorporating five traditional prognostic factors: ER, PR, LVI, nuclear grade, and Ki-67. An independent prospective validation for the present nomogram is underway to confirm its accuracy.

**Legal entity responsible for the study:** Saebyul Lee

**Funding:** Asian Medical Center

**Disclosure:** All authors have declared no conflicts of interest.
Methods: We examined 76 patients (75 women and one man) with BRC 52 concurrent and 24 metastatic. Paraffin tumors (n = 155) with informative targeted NGS data were histologically reviewed and subtyped with immunohistochemistry (IHC). In a patient subset, peripheral blood genetic samples were obtained with the same panel and/or upon testing for cancer predisposing genes (germline testing). We analyzed coding mutations (amino acid changing, minor allele frequency <0.1%) and single nucleotide polymorphism (SNP) zygosity.

Results: Breast histology and tumor IHC subtype were concordant in 85% and 64% of bilateral cases, respectively. We identified 258 mutations in 80 tumors (54 patients). TP53 and PIK3CA were the most frequently mutated genes (19% and 14%, respectively), followed by CDH1, GATA3 and MLH3. TP53 mutation rate was significantly higher in metastatic tumors (p < 0.001), TNBC and HER2-enriched IHC subtypes (both p < 0.001), higher Ki67 labeling (p = 0.002) and in patients of younger age (p = 0.01). Hypermutated tumors, all carrying TP53 mutations, were diagnosed as the first incidence in 5 patients, the corresponding metastasis were mutation poor without TP53 involvement. Among the 202 comparable mutations in matched tumors, only 10 were common bilaterally. Although SNPs were shared bilaterally at a high rate, SNP zygosity status was less preserved in metastatic compared to concurrent disease (p = 0.04). Ten of the 29 patients with germline testing data carried pathogenic mutations, 9 in BRC1 and one in TP53.

Conclusions: Clonal origin is revealed in few patients for the examined genes. The present findings support that BRC tumors are mostly bilateral tumors arising in the same patient, which justifies current clinical practice.

Clinical trial identification: N/A

Legal entity responsible for the study: Hellenic Cooperative Oncology Group

Funding: Hellenic Cooperative Oncology Group internal research grant

Disclosure: All authors have declared no conflicts of interest.

Prospective evaluation of the impact of the 21-gene recurrence score® assay on adjuvant treatment decisions for women with node-negative breast cancer in Ontario, Canada

T. Petrella1, E. Slodkowska1, M. Hew-Shue1, C. Chao2, A. Eisen1

recommendations changed from upfront CT pre-assay, to endocrine therapy only (62). The most significant change was in the group with a low RS (<18): 45% of the assay affected patients...
21% of group II). The BCVY group showed worse prognosis among lymph node-positive patients (p = 0.02). The status of lymph nodes post-surgery seems to be the only factor related to BCVY patients. In group I, we objectively also a statistically significant relationship between axillary involvement, HR2 HER2 positive subtype and disease relapse (p = 0.03). We also observed a shorter time between single and double polymorphisms in NQO1, CYP1A1, ERCC1, ERCC2, FGF4, TP53, ERBB2, ABCB1 and 5-years recurrent rate.

Methods: Operated breast cancer patients followed in Gaziantep University Oncology Hospital between June 2004 and June 2011 were analyzed retrospectively. Clinicopathologic variables and administered treatment schemes were noted. Blood samples were taken and genomic DNA was extracted. Genotyping the Fluidigm Digital Dynamic Array was performed and "genomic DNA a 96.6 dynamic array on the BioMark HD system" was used for evaluation. Relations of these parameters with 5-year recurrence risk were analyzed with univariate and multivariate regression model.

Results: 286 patients were included in this study. According to tumor size, recurrence rates of T1/T2/T3 and T4 patients were 17.1%/17.2%/34.5% and 18.2% respectively (p = 0.045). According to lymph node status, recurrence rates of N0/N1/N2 and N3 patients were 12%/13.4%/32.6% and 51.4% respectively (p < 0.001). The relation of tumor size (T), Her-2 status, p53 and ABCB1 gene mutations with recurrence in patients with node positive disease was evaluated in multivariate analysis. Accordingly, both P53 (p = 0.02) and ERCC1 genes (p = 0.027) was found to be related with patients with node positive disease was evaluated in multivariate analysis. Accordingly, tumor size (T), Her-2 status, p53 and ABCB1 gene mutations with recurrence in patients were 12%/13.4%/32.6% and 51.4% respectively (p < 0.001). The relation of ERCC1 and p53 genes can predict the 5-year recurrence risk of lymph node positive breast cancer patients.

Legal entity responsible for the study: Tahal Kus

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 186P Gene polymorphisms

<table>
<thead>
<tr>
<th>Gene</th>
<th>N</th>
<th>SNP</th>
<th>Genotype</th>
<th>P-value OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4*</td>
<td>261</td>
<td>rs2740574</td>
<td>GG vs AA and AG</td>
<td>0.239 1.515</td>
<td>0.567-4.052</td>
</tr>
<tr>
<td>NQO1</td>
<td>280</td>
<td>rs1800566</td>
<td>AA vs AG and GG</td>
<td>0.731 0.696</td>
<td>0.328-1.474</td>
</tr>
<tr>
<td>ABCB1*</td>
<td>255</td>
<td>rs1045642</td>
<td>CC and CT vs TT</td>
<td>0.916 0.958</td>
<td>0.426-2.152</td>
</tr>
<tr>
<td>ERCC1</td>
<td>272</td>
<td>rs2312935</td>
<td>AG and GG vs AA</td>
<td>0.031 3.630</td>
<td>1.051-12.537</td>
</tr>
<tr>
<td>ERCC2</td>
<td>212</td>
<td>rs131891</td>
<td>AA vs AC and CC</td>
<td>0.708 1.184</td>
<td>0.490-2.864</td>
</tr>
<tr>
<td>ERBB2**</td>
<td>61</td>
<td>rs1136201</td>
<td>AA vs AG and GG</td>
<td>0.025 4.278</td>
<td>1.147-15.952</td>
</tr>
<tr>
<td>P53</td>
<td>239</td>
<td>rs1042522</td>
<td>CC vs GC and GG</td>
<td>0.040 2.573</td>
<td>1.022-6.475</td>
</tr>
<tr>
<td>FGF4</td>
<td>247</td>
<td>rs351855</td>
<td>AA vs AG and GG</td>
<td>0.342 0.696</td>
<td>0.328-1.474</td>
</tr>
</tbody>
</table>

* Only for the patients who received antracyclin and taxane based treatment. ** Only for the patients who received anti Her-2 treatment. SNP: single nucleotide polymorphism, OR: odds ratio

Conclusions: ERCC1 and P53 genes can predict the 5-year recurrence risk of lymph node positive breast cancer patients.

Legal entity responsible for the study: Tahal Kus

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 187P Intrinsic subtype and response to neoadjuvant chemotherapy with carboplatin and docetaxel (TCB) in triple-negative breast cancer (TNBC)

<table>
<thead>
<tr>
<th>Case ID</th>
<th>Subtype</th>
<th>Number of TCB treatment</th>
<th>Pathological complete response (%)</th>
<th>pCR (number of patients)</th>
<th>Number of patients</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LAR</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>Basal</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>LBC</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>50%</td>
</tr>
</tbody>
</table>

Background: Triple-negative breast cancer (TNBC) is a heterogeneous disease with distinct molecular subtypes. A luminal androgen receptor subgroup dependent on AR expression has been recently defined in a gene-expression study by Lehmann et al. We aimed to explore the clinical relevance of this AR dependent subtype in TNBC determining differences in response to neoadjuvant chemotherapy.

Methods: In a population of 116 patients (39% from GEICAM/2006-03 trial) treated with neoadjuvant anthracyclines and taxanes +/- carboplatin, tumor DNA was obtained from FFPE pre-treatment tumor biopsies. Lehmann subtypes were determined by gene expression profiling with HTA2.1 array (Illumina) and the classification tool TNBCtype. Breast cancer intrinsic subtypes according to PAM50 test were also determined with an nCowner Analysis System (Nanosting Technologies). The association of the different subtypes with pathological complete response (pCR) was explored using Fisher’s exact test and logistic regression.

Results: The global rate of pCR of TNBC patients was 38.8%, and it was unevenly distributed within Lehmann’s subtypes. Basal-like subtypes had the highest rates (BL1 = 53%, BL2 = 46%) and the luminal-androgen receptor (LAR) the lowest (14%). As it has been previously described that MSL is enriched in normal tissue, we performed this analysis with and without MSL subgroup, obtaining a significant association between LAR subtypes and pCR when MSL was included (p = 0.35 and p < 0.045, respectively). Most patients were classified as basal-like according to PAM50 except those included in LAR subtype that were also HER2-enriched (33.3%) and Luminal A (11.1%).

Conclusions: Our results suggest that there is a high genetic diversity within TNBC, mainly due to a luminal androgen receptor subtype that includes an elevated percentage of non-basal-like tumors. The LAR subtype is associated with a lower rate of pCR probably because almost half of them don’t have basal-like characteristics (HER2 neutral anti HER2 therapy and Luminal). Taking into account this specific subtype it could be necessary to use a new TNBC classification.

Legal entity responsible for the study: FIMABIS-GEICAM

Funding: FIMABIS

Disclosure: All authors have declared no conflicts of interest.

Background: Triple-negative breast cancer (TNBC), while sensitive to chemotherapy, remains a challenge due to its differential response to treatment and poor prognosis. In a population of TNBC patients treated with NACT with docetaxel plus carboplatin (TC), we evaluated the predictive value of the intrinsic subtype by PAM50.

Methods: Pathological response was defined as complete response (cCR) in residual cancer burden method, with pathological complete response (pCR) considered as lack of invasive tumor in breast plus axilla (ypT0/isypN0). Intrinsic subtype was determined by PAM50 gene expression analysis.

Disclosures: A. Galvez-Bernal, C. de la Torre, G. Molina, A. Fernandez, M. de la Haba, and E. Ferreira have received research funding from the Spanish National Research Council (FEDER) and the European Commission (Programme H2020). R. de la Haba has received research funding from the Spanish National Research Council (FEDER) and the European Commission (Programme H2020).

Conclusions: pCR rate was significantly higher for the Basal subtypes than for the LAR subtype (p = 0.02). These results suggest that the use of the new intrinsic subtype classification could be useful in the management of TNBC patients.
Breast cancer prognosis after neoadjuvant chemotherapy for breast cancers: molecular downstaging, proliferation, and endocrine sensitivity importance

1Medical Oncology, APHP, CancerEst, Tenon University Hospital, Paris, France, 2Pathology, APHP, CancerEst, Tenon University Hospital, Paris, France, 3Cytogenetics, APHP, CancerEst, Tenon University Hospital, Paris, France, 4Radiology, APHP, CancerEst, Tenon University Hospital, Paris, France

Background: Pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) is a reasonable prognostic factor for all breast cancer (BC) subtypes. We assessed the importance of other clinical and pathological parameters as prognostic factors after NAC.

Methods: From 2005 to 2014, 236 non metastatic BC patients were consecutively treated in our institution with the same NAC combining sequentially anthracyclines-cyclophosphamide followed by taxanes (trastuzumab was added in HER2 positive population). All the data concerning patient population, initial tumor stage, pathological characteristics on biopsy, as also after surgery were collected. Pathological analysis was centralized. pCR was defined according to UICC criteria. Disease free survival (DFS) was calculated since the day of first surgery. Analyses employed logistic regression and Cox proportional hazard models.

Results: Of 236 patients, 140 (59%) were ER positive, 44 (19%) were triple negative and 52 (22%) were HER2 positive. The overall pCR rate was 26.3%. We found that High Ki67, low PgR and low ER are associated with a pCR. In the group of ER positive patients, a cut-off of Ki67 at 30% was associated in a multivariate analysis with the probability of a pCR (>30% vs <30% - odds ratio = 3.9, IC 95% = 1.13-8.91, p = 0.026) as well as ER 90% (>90% vs 90%-OR = 0.24, IC 95% = 0.07-0.68, p = 0.017). Even if pCR was not achieved, we found a molecular down-staging particularly among the luminal B population (defined by IHC criteria) (58.1% change into luminal A).

Conclusions: These data suggest that particularly in HR positive population, pathological characteristics of residual tumor (ER, PgR, Ki67) might be very informative for clinical outcome of patient that did not achieve pCR after NAC. Legal entity responsible for the study: None

Funding: None

Table: 188P RCB distribution across subtypes (Symmans et al, JCO 2007)

<table>
<thead>
<tr>
<th>%</th>
<th>All (n = 95)</th>
<th>Basal-like (n = 79)</th>
<th>Non-Basal (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>44.2</td>
<td>50.6</td>
<td>12.5</td>
</tr>
<tr>
<td>RCB I</td>
<td>11.6</td>
<td>10.1</td>
<td>18.8</td>
</tr>
<tr>
<td>RCB II</td>
<td>30.5</td>
<td>29.1</td>
<td>37.5</td>
</tr>
<tr>
<td>RCB III</td>
<td>13.7</td>
<td>10.1</td>
<td>31.2</td>
</tr>
</tbody>
</table>

Effect of body mass index (BMI) on response to neoadjuvant therapy in human epidermal growth factor receptor 2 (HER2) positive breast cancer (BC): Analysis from NeoALLTO trial

1Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, 2Statistics, Frontier Science, Kincraig, UK, 3U.O.C. Oncologia, Ospedale A. Perrino, Bologna, Italy, 4Department of Hematology & Oncology, Memorial Sloan Kettering Cancer Center, New York, USA, 5Gynecology, Ulm Medical University, Germany, 6Breast Cancer Translational Research Laboratory, Institute Jules Bordet, Brussels, Belgium, 7Novartis Oncology, Novartis Pharma AG, Basel, Switzerland, 8Medicine Department, Institute Jules Bordet, Brussels, Belgium, 9Medical Oncology, Institute Jules Bordet, Brussels, Belgium

Background: Obesity is a risk factor for the development of BC in postmenopausal women and has been linked to increased risk of recurrence and death in BC patients (pts). Herein, we aimed to investigate the prognostic and predictive role of obesity in HER2 positive BC pts treated with neoadjuvant anti-HER2 therapies.

Methods: NeoALLTO enroled 455 women with invasive HER2 positive BC and compared rates of pathologic complete response (pCR) to neoadjuvant lapatinib/trastuzumab or their combination given alone for 6 weeks and then combined with weekly paclitaxel. In the present analysis, pts’ outcomes in terms of event free survival (EFS), overall survival (OS) and pCR rates were evaluated according to hormone receptor (HR) status and BMI. We used the World Health Organisation (WHO) classification for BMI categories.

Results: 14 pts (3.1%) were underweight (BMI <18.5 kg/m2), 220 (48.8%) had a normal BMI (18.5-25 kg/m2), 137 (30.2%) were overweight (BMI 25.0-30.0 kg/m2) and 83 (18.3%) were classifiable as obese (BMI >30.0 kg/m2). The impact of BMI on pCR rate was studied by collapsing BMI into two groups, above and below 25 kg/m2. There were no apparent effects of BMI when an effect independent of HR status was fitted [odds ratio (OR) for effect of normal BMI relative to high 1.12, 95% confidence interval (CI) 0.72-1.79]. However, there was a significant interaction between BMI and HER status (p = 0.034). In the interaction model, a modest effect of BMI was seen in HR negative pts (OR 2.02, 95% CI 1.04-3.92), whereas in HR negative pts there were no apparent effects (OR 0.79, 95% CI 0.45-1.39). BMI did not predict either EFS or OS in any treatment arms or HR subgroups, but NeoALLTO was not powered for these endpoints.

Disclosure: I. Gilgort: Consulting or advisory role: Eisai, Roche/Genentech, Novartis, Teva, Prizer. Honoraria: Eisai, Roche/Genentech, Novartis, Teva, Genomic Health. Prizer Speaker’s bureau: Eisai, Roche/Genentech. All other authors have declared no conflicts of interest.

Measurement of molecular biomarkers to predict tumor response in estrogen receptor positive breast cancer after dose-dense (biweekly) paclitaxel/carboplatin neoadjuvant chemotherapy

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1The second department of breast cancer, Guangdong General Hospital, Guangzhou, China, 2The Second Department of Breast Cancer, Guangdong General Hospital, Guangzhou, China

Background: Dose-dense (biweekly) paclitaxel/carboplatin (PC) is neoadjuvant chemotherapy (NCT) for operable breast cancer is feasible and efficient. This study was to analysis the relationship between the molecular biomarkers and tumor response in estrogen receptor (ER) positive breast cancer.

Methods: 84 ER-positive breast cancer patients treated with Dose-dense (biweekly) paclitaxel/carboplatin NCT were analyzed for expression of progesterone receptor (PgR), Her2, Ki67, HER2, Bcl-2 by immunohistochemistry (IHC), these data were used to test whether these biomarkers can predict tumor response. The primary endpoint was a pathologically complete response (pCR). The second endpoint was the change in tumor size between pre and post NCT.

Results: Univariate analysis showed that HER2 positive (53.85% vs 8.62%, p = 0.019), Tau negative (40.91% vs 16.13%, p = 0.017), BCL-2 negative (48.15% vs 10.53%, p < 0.01) were independent pCR predictive biomarkers. Tumor size was significantly reduced in HER2 positive (p = 0.001, high-level Ki67 (p = 0.007), Tau negative (p = 0.002), BCL-2 negative (p = 0.008) breast cancer.

Conclusions: This study investigates the value of traditional biological markers, Bcl-2 and Tau in ER-positive patients treated with dose-dense (biweekly) paclitaxel/carboplatin NCT.

Clinical trial identification: NCT02059876

Legal entity responsible for the study: N/A

Funding: Guangdong General Hospital

Disclosure: All authors have declared no conflicts of interest.
Conclusions: The present study found no significant impact of BMI in response to neoadjuvant therapy in the whole HER2 positive population. However, a significant correlation was seen in pts with HR positive tumours. Our data potentially pave the way to future research in developing combined therapeutic strategies for HER2 positive luminal BC, with the intent of obtaining a complete blockade of the driving growth factor signals via both HER2 and HRs.

Clinical trial identification: NCT00553358

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori

Funding: None

Disclosure: I. Bradbury: Ian Bradbury’s institution has received funding from GlaxoSmithKline and Roche. J. Baslega: Honoraria received from Roche. S. Sarp: Novartis AGM. Piccart: Honoraria received from GlaxoSmithKline and Roche. research funding to Institution from GlaxoSmithKline.E. de Aramburu: Advisory board and travelling grant from GlaxoSmithKline, speaker for Roche. S. Ciomso: Speaker for GlaxoSmithKline. All other authors have declared no conflicts of interest.

192P Effect of body mass index on pharmacokinetics of paclitaxel in women with early breast cancer

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Background: It is common practice to dose paclitaxel according to body surface area (BSA) in women with early breast cancer (EBC). However, there is scant information on actual drug exposure in overweight/obese women and whether actual or modified weight should be used in calculating BSA. The present study evaluates effect of Body Mass Index (BMI) on pharmacokinetic (PK) profile of paclitaxel.

Methods: EBC patients in two BMI groups (normal, 18.24-25 kg/m² and overweight/obese, ≥25 kg/m², respectively) were enrolled. All patients received single agent paclitaxel at 175 mg/m² q3wks. The two groups were matched for age, albumin and bilirubin levels using a minimization technique. Sparse PK sampling was performed at 7 time points from time 0 until 24 hours of starting paclitaxel infusion in cycle 1. Paclitaxel concentration was measured using a validated LC/MS/MS method. PK data was modeled using WinNonlin software and PK parameters were compared using Student’s t-test. Covariate effect on paclitaxel PK was evaluated by population PK analysis using NONMEM software.

Results: Thirty-six patients (18 in each group) were enrolled with mean BMI of 21.5 ± 2.0 and 28.2 ± 2.3 kg/m², mean BSA of 1.43 ± 0.11 and 1.69 ± 0.14 and mean paclitaxel dose of 250 ± 18 and 293 ± 20 mg, in normal and overweight/obese groups, respectively. The two groups were comparable with respect to serum albumin, bilirubin, hemoglobin and performance status. PK data was well described by a two-compartment nonlinear clearance model. Normal and overweight/obese groups had comparable AUC(0-∞) (26 ± 14 vs. 24 ± 13 μg/ml-hr, p = 0.657), Cmax (7.6 ± 4 vs. 6.6 ± 3 μg/ml, p = 0.563), volume of distribution (69 ± 47 vs. 68 ± 34 L/m², p = 0.938) and clearance (8.9 ± 4.8 vs. 9.7 ± 5.4 L/hr/m², p = 0.637), respectively. Population PK analysis showed a significant positive correlation between BMI and paclitaxel clearance while no other covariate was significant. There was no significant difference in toxicity between the two groups.

Conclusions: There is no significant difference in paclitaxel exposure between normal and overweight/obese women with EBC when dosed according to BSA that is calculated using actual body weight. The latter should be used when calculating paclitaxel dose in overweight/obese patients.

Clinical trial identification: Clinical trial registry of India Identifier: CTRI/2015/09/ 001193

Legal entity responsible for the study: Tata Memorial Centre, Mumbai

Funding: The study was funded by Tata Memorial Centre, Mumbai, through the intramural funds

Disclosure: All authors have declared no conflicts of interest.

193P Effect of body mass index on the outcome of stage I-II triple negative breast cancer

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2Department of Medical Oncology, Hacettepe University Faculty of Medicine, Ankara, Turkey
3Medic Oncology, Ankara Nurun Education and Research Hospital, Ankara, Turkey

Background: Breast cancer classified mostly into 4 major molecular subtypes based on the expression of receptors for estrogen (ER), progesterone (PR), and human epidermal growth factor (HER-2) and Ki-67 staining. Triple-negative breast cancer (TNBC) refers to a subgroup of patients with no expression of ER, PR or HER-2, and accounts for 10-20% of all newly diagnosed breast cancer cases. Although obesity is known to be an important risk factor for development of breast cancer and affects the prognosis unfavorably especially in luminal type tumours the effect of obesity in TNBC was not known exactly. In this trial we aimed to investigate the effect of body mass index (BMI) on the outcome of TNBC.

Methods: Between 1998-2013 years from 4584 patients with invasive breast cancer patients who had non-metastatic TNBC with baseline BMI at the time of diagnosis were enrolled to this study (n = 371). Patient’s demographics, including survival data and tumor characteristics were obtained from medical charts. Patients with BMI ranging between 18.5 and 21.9 kg/m² were considered as normal weight patients (Arm A, n = 122), and patients with a BMI ranging ≥25 kg/m² were grouped as overweight and obese patients (Arm B, n = 249). Kaplan-Meier survival analysis was carried out for disease free survival (DFS) and overall survival (OS).

Results: The median follow up of patients was 44.1 months. Median age of patients was 43 (23-81) and 49 (20-82) in group A and B, respectively (P = 0.001). There were no apparent differences in histological type, grade, axillary lymph node involvement, extraareolar extension, perineural invasion, lymphovascular invasion, menopausal status, Treatment patterns such as chemotherapy and radiation were similar. But significantly TNM stage 3 was seen significantly higher in Group B patients (26.9% vs 15.8%, P = 0.01). In Group A, 5-year diseases free survival (DFS) rate was 89.3% whereas it was 75.0% in Group B (P = 0.05). In Group A, 5-year overall survival (OS) rate was 93.0% whereas it was 81.0% in Group B (P = 0.01).

Conclusions: In our study, like luminal A and B tumors, obesity is associated with poorer DFS and OS in stage 1-3 TNBC patients.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

194P Body mass index as a prognostic factor in operable breast cancer patients treated with adjuvant anthracyclines with or without taxanes

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1Clinical Oncology and Nuclear Medicine, Mansoura University Hospital School of Medicine, Mansoura, Egypt
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3Medical Oncology, Mansoura University Faculty of Medicine, Mansoura, Egypt

Background: Breast cancer is the most frequent invasive tumor in women. Obesity is a risk factor for several types of cancer, including breast cancer. Obesity is an unfavorable prognostic factor in breast cancer regardless of menopausal status and treatment protocol. The aim of the study was to assess the effect of obesity on prognosis in operable breast cancer patients according to pathologic subtypes.

Methods: A retrospective analysis of 500 operable breast cancer patients received adjuvant anthracyclines with or without taxanes enrolled in the period between Sep 2011 and Sep 2013, the primary end point was to assess the prognostic effect of body mass index (BMI) on disease recurrence, breast cancer mortality (BCM), and overall mortality (OM). The secondary end point was to detect the difference by breast cancer pathologic subtypes (ER, PR positive/HER2 positive, ER, PR positive/HER2 negative, ER, PR negative/HER2 positive, and triple negative)

Results: Analyses were adjusted for age, tumor size, grade, nodal status, menopausal status, hormone receptors and HER2 receptor status, surgery and chemotherapy regimens. Obese patients (BMI = 30-39.9 kg/m²) had similar prognosis as that of normal weight patients (BMI <25 kg/m²) (control group) in terms of recurrence (HR 1.07 95% CI 0.8-1.32 P = 0.42), BCM (HR 1.04 95% CI 0.84-1.28, P = 0.84) and OM (HR 0.96, 95% CI 0.79-1.18, P = 0.73). Patients with severe obesity BMI ≥40 kg/m² had a significantly increased risk of recurrence (HR 1.25, 95% CI 1.1-1.59, P = 0.05), BCM (HR 1.39, 95% CI 1.1-1.74; P = 0.05) and OM (HR 1.3, 95% CI 1.05-1.72; P = 0.02) compared to the control group. The prognostic effect of severe obesity showed no remarkable variation among pathologic subtypes.

Conclusions: Severely obese breast cancer patients with a BMI ≥40 kg/m² treated with anthracyclines with or without taxanes had a worse prognosis in terms of recurrence, BCM & OM than patients with a BMI <25 kg/m². The risk was not altered in different pathologic subtypes.

Legal entity responsible for the study: Mansoura University

Funding: Mansoura University

Disclosure: All authors have declared no conflicts of interest.

195P Is there an impact of body mass index on the breast cancer stage at initial diagnosis?

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Background: Some data suggest that there is a correlation between body mass index (BMI) and tumor stage in some biological subtypes. Others don’t. The main objective of our study was to analyze the association between BMI and tumor stage according to the molecular profile.

Methods: Data were collected from the 2014 prospective database of breast cancer at the National Oncology Institute in Rabat, Morocco. The mass body index (BMI) was
calculated by the formula: body weight (kg)/height (m)^2. SPSS was used for statistical Analysis, tests used are analysis of variance, comparison of mediums, and test Khi-two.

**Results:** 481 patients were eligible. Medium of age was 48.9 years. 21.7% of tumors were HER2, 17.7% Triple negative and 60.6% luminal. The tumors were: T1 = 21.9%, T2 = 47.9% T3 = 11.7%, T4 = 12.7% T4c = 5.6%. For stages: I: 11.9%, II: 24.4%, III: 20.4%, IIIA: 15.8%, IIIB: 10.2%, IIIC: 10%, IV: 7.3%. The tumors grading: Grade 1: 8.7%, Grade 2: 57.9%, Grade 3: 33.6% all correlation between BMI and other parameters and was negative even in triple negative cancers.

<table>
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<th>Table: 198P</th>
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<tr>
<td><strong>BMI Profile</strong></td>
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<td>Underweight</td>
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<td>Normal</td>
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<td>Overweight</td>
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<td>Obesity moderate</td>
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<td>Severe obesity</td>
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<td>Morbid obesity</td>
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<td>Statistical correlation between BMI and:</td>
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<tr>
<td>Tumor size</td>
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<td>Tumor stage for all subtypes</td>
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<tr>
<td>Tumor stage for luminal cancers</td>
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<tr>
<td>Tumor stage for HER2 positive</td>
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<tr>
<td>Tumor stage for triple negative cancers</td>
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<td>Expression estrogen hormone receptors</td>
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<td>Expression progesterone hormone receptors</td>
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<td>Expression HER2</td>
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**Conclusions:** Our study suggests that there is no correlation between BMI and tumor stage regardless of the biological subtypes. Others studies are needed to confirm our results.

**Legal entity responsible for the study:** National Institute of Oncology Rabat Morocco

**Funding:** National Institute of Oncology Rabat Morocco

**Disclosure:** All authors have declared no conflicts of interest.

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**Effect of using different antihypertensive drugs on demographic and clinico-pathological characteristics of breast cancer**

**Background:** There is limited data about the association of breast cancer and with a selective anti-HT usage. Thus, we aimed to investigate relationship between anti-HT usage and clinico-pathological properties of breast cancer.

**Methods:** Breast cancer patients from 1998 to 2015 were retrospectively analyzed. Patients who were taking oral antihypertensive drugs more than 12 months at the time of breast cancer diagnosis were enrolled as anti-HT users (n = 923), where the patients matched with the same age who were not taking oral anti-HT were included as a control group (n = 923).

**Results:** A total of 946 patients with breast cancer were included in this study. 923 patients received an oral anti-HT treatment more than 1 year at the time of breast cancer diagnosis, and 923 patients were considered as non-users. The median follow-up of patients was 57 months. Median age of both groups were 57 (23–89). There were no apparent differences in histological type, term of baseline tumor size, grade, axillary lymph node involvement, extracapsular extension, lymphovascular invasion, type of surgery, menopausal status and hormonal receptor status between both groups.

In hypertensive group the history of obesity, hyperlipidemia and diabetes were significantly higher than control group. But perineural invasion positivity and HER2 expression was significantly lower in patients with anti-HT users group (P = 12.9% vs 8.8%, P = 0.009, HER2 positivity, 19.5% vs 15.3%, P = 0.02). Significantly lower incidence of T3-T4 tumor and TNM stage were seen in patients with anti-HT users group compared to nonusers. (Stage 3: 4. 33.6% vs 38.8%, P = 0.04). In survival analysis, in oral anti-HT users 5-year DFS rate was 80.3%, whereas it was 75.4% in non-users (P = 0.14). Median OS could not be obtained due to low events in both groups but 5-year survival rate in oral anti-HT users was 89.6%, whereas in non-users it was 86.3% (P = 0.01). In oral anti-HT group there was no effect on recurrence and survival between different anti-HT treatments.

**Conclusions:** In our study, despite higher body mass index and higher incidence of comorbidities in patients with oral anti-HT users, a trend of improvement was observed in terms of DFS and significantly improvement in OS was observed.

**Legal entity responsible for the study:** N/A

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**Effect of using different antidiabetic drugs on demographic and clinico-pathological characteristics of breast cancer**

**Background:** Among 20 % of patients diagnosed with breast cancer have also diabetes mellitus as a comorbid condition. There is growing evidence that the use of metformin in diabetic patients was associated with lower risks of cancer. In this study, we aimed to investigate retrospectively the demographic and clinico-pathological characteristics of patients with different antidiabetics (AD) users at the time of breast cancer diagnosis.

**Methods:** From 3890 breast cancer patients who were taking AD drugs more than 12 months at the time of breast cancer diagnosis were enrolled (n = 378). Patients were classified as Group 1 if they treated only with metformin, Group 2 another oral AD, Group 3 oral AD combination, Group 4 insulin plus oral AD and Group 5, if they treated with insulin only.

**Results:** Median age of 378 patients diagnosed with breast cancer and diabetes was 58 (23-92). The median follow-up of patients was 47 months. There were 128 patients (38.8%) in Group 1, 106 patients (32.1%) in Group 2, 103 patients (30.3) in Group 3, 27 patients (9.8%) in Group 4 and 56 patients (15.7) in Group 5. The 5 groups were well-balanced and there were no apparent differences in histological type, term of baseline tumor size, grade, axillary lymph node involvement, extracapsular extension, perineural invasion, lymphovascular invasion, type of surgery, menopausal status, HER2 positivity and hormonal receptor status between 5 groups. Both estrogen and progesterone receptor positivity were same between 5 groups. Treatment patterns such as hormonal treatment, chemotherapy and radiotherapy were also similar. Similarly, distribution of TNM stages were same between groups. 5-year DFS rates were 81.9%, 77.3%, 79.3%, 72.5% and 61.9% in Groups 1-5, respectively (P = 0.006). 5-year OS rates were 89.3%, 92.3%, 92.9%, 81.8% vs 67.7% in Groups 1-5, respectively. (P = 0.002).
Conclusions: In our study, patients treated with insulin alone or combination have significantly worse OS and borderline significant worse DFS compared to diabetic breast cancer patients treated with oral AD medications. The insulin-sensitizing effect of metformin may play a major role in its anti-cancer activity.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

19SP Impact of vitamin D3 replacement therapy on clinical outcomes and survival rates in patients with early stage breast cancer

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Background: In literature some studies suggested that in patients having solid malignancies poor prognosis is associated with vitamin D3 deficiency and replacement of vitamin D3 might have positive impact on prognosis. However, some of the results of the studies were against this suggestion. Therefore, in the current study we aimed to compare the clinical, pathological features and survival rates in patients with early breast cancer having regular vitamin D3 replacement or not.

Methods: In between October 2002 and October 2015, patients with early stage breast cancer were included in study population. The patients were divided into two groups according to their regular vitamin D3 replacement status. Vitamin D3 doses that the patients were receiving were calculated to increase the levels beyond 20 ng/mL (50 nmol/L). The patients with metastasis/relapse or secondary primaries were excluded.

Results: In vitamin D3 and non-vitamin D3 group 92 and 2864 patients were included. Median follow up time was 60 (min:1-max:420) months. Mean age at time of diagnosis, rate of patients with postmenopause, T1 tumor and breast conserving surgery was significantly higher in vitamin D3 replacement group compared with non-vitamin D3 group (p < 0.05) (Table 1). Disease free survival rate was similar in both patients group. In vitamin D3 replacement and non-vitamin D3 group overall survival rates in 1st, 3rd and 5th year was in order 98% vs 99%; 96% vs 96%; 95% vs 92%; the difference was not significant (p = 0.16).

Conclusions: Regular vitamin D3 replacement therapy did not have effect on prognosis of patients with early breast cancer. Most of the postmenopausal and older aged patients with early breast cancer received vitamin D3 replacement most probably due to higher rate of osteoporosis in this aged patient group.

<table>
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<tr>
<th>Table: 19SP Clinical and pathological features of early breast cancer patients in vitamin D and non-vitamin D group</th>
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<tr>
<td><strong>Regular Vitamin D Replacement Group</strong> (n = 92)</td>
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<tr>
<td>Mean Age</td>
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<tr>
<td>Invasive Histopathological Subtype</td>
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<tr>
<td>Grade</td>
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<td>Body Mass Index &gt;25 kg/m²</td>
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<td>Menopausal Status</td>
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<tr>
<td>Breast Surgery</td>
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<td>Estrogen Receptor</td>
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<td>Progesterone Receptor</td>
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<td>Her-2 Status</td>
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<td>TNM Tumor Stage</td>
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<td>TNM Nodal Stage</td>
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Legal entity responsible for the study: Ankara Numune Education and Research Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

200P Metformin anti-proliferative effect on a cohort of non-diabetic breast cancer patients

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Background: Whereas the preoperative period is increasingly popular for the clinical investigation of new biological agents and also establishment of K67 as an intermediate proliferative marker of treatment benefit.

Methods: We design a prospective randomized controlled study about metformin efficacy in the window time between biopsy and definite surgery. Our primary endpoint was changes of K67. Patients neither had indication of neoadjuvant chemotherapy, nor involved with diabetes mellitus. They followed during the time period of biopsy and definitive surgery. Metformin (1500mg/day) was prescribed to intervention group from pathology report to the night before surgery. Control group were patients with the same inclusion criteria who did not receive any drug.

Results: From 50 patients enrolled 5 excluded. Four before using any pills and one in the first day of taking metformin. 25 had been received metformin for median time of 2.8 weeks. Controlled group included 20 patients who followed in the window time. There were not statistically significant differences between two groups regarding baseline clinical and tumor characteristics such as age, stage, grade, ER, PgR, HER2 status, time and type of surgery. However, immunohistochemistry study showed decrease of median K67 from 35.14 to 26.4 in the intervention group and increase from 24.5 to 30.6 in the control group. Both of these results were statistically significant. Although mild gastrointestinal symptoms were seen in 30% of cases, generally patients tolerated metformin very well. There was a correlation between metabolic anti-proliferative effect and glucose and insulin metabolism.

Conclusions: In the present study metformin prescription in the short period of time between biopsy and definite surgery had shown inhibition of breast cancer cell growth. We found relationship between metformin anti-proliferative effect and glucose and insulin metabolism.

Clinical trial identification: code number in Research Deputy of Tehran University is 92-03-51-24050

Legal entity responsible for the study: Research Deputy of Tehran U Medical Sciences

Funding: Research Deputy of Tehran U Medical Sciences

Disclosure: B. Behrouz. I declare there is no conflict of interest about this research. All other authors have declared no conflicts of interest.

201P Dyslipidaemias after adjuvant chemotherapy in young Chinese breast cancer patients

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Background: Adjuvant chemotherapy improves outcome of patients with early breast cancer. However, chemotherapy may be associated with long term toxicities, there is limited data on the incidence of dyslipidaemias after adjuvant chemotherapy. In this prospective cross-sectional study, the objectives were to determine the incidence of dyslipidaemias and the associated factors among young premenopausal Chinese breast cancer patients after adjuvant chemotherapy.

Methods: Eligibility criteria include Chinese breast cancer patients of stage I-II, younger than 45 years at diagnosis, having received adjuvant chemotherapy, within 3-10 years after the diagnosis of breast cancer. Patients' characteristics, anti-cancer treatments, body weight and height at the time of breast cancer diagnosis (i.e. prior to chemotherapy) were collected. At study entry, patients had body weight and fasting blood lipids determined; incidence of chemotherapy-related amenorrhea (CRA) and menopause were determined based on detailed menstrual history. Dyslipidaemia was defined according to US National Cholesterol Education Program. Analysis was conducted to identify factors associated with dyslipidaemia.

Results: 280 patients were studied; the median time from breast cancer diagnosis was 5.0 years. 91.1% developed CRA; 48.9% had become menopausal and 10% were peri-menopausal. At the time of study entry; the mean weight gain was 1.8 kg from 24.5 to 30.6 in the control group. Both of these results were statistically significant. There were no statistically significant differences between two groups regarding BMI, age, stage, grade, and chemotherapy.

Conclusions: At a median of 5 years after breast cancer diagnosis and adjuvant chemotherapy, dyslipidaemias were frequent. Clinicians need to increase awareness of this aspect and interventional studies including lifestyle modifications are warranted to optimize long-term care for these patients.

Legal entity responsible for the study: Chinese University of Hong Kong
Funding: Hong Kong Cancer Fund and Madam Diana Hon Fun Kong Donation for Cancer Research

Disclosure: All authors have declared no conflicts of interest.

**Abstract 203P**

### Influence of adjuvant chemotherapy on anti-müllerian hormone (AMH) level in patients younger than 35 years treated for an early breast cancer (EBC)

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**Background:** The overall negative influence of chemotherapy on ovarian reserve is well established. Since few years, AMH is used as a fertility marker, both in assisted reproductive technology and oncology. Surprisingly, if young patients are the most ones concerned with fertility questions, the specific impact of adjuvant chemotherapy for EBC in this population is unknown. In this context, we analysed AMH in patients ≤ 35 years presenting an EBC, before any treatment, at 1, 3 and 5 years after diagnosis.

**Methods:** This is a monocentric retrospective study. Patients aged ≤ 35 years treated for EBC between 2008 and 2014, with frozen heparinized plasma samples before and after chemotherapy exposure and with a written consent for research use were included. All analysis were performed simultaneously with Elecsys® AMH assay (Roche Diagnostics). Statistics were performed using Mann-Whitney or Wilcoxon tests.

**Results:** Fifty-four patients were included, 23 (43%) had a triple negative and 29 (54%) hormone receptor positive breast cancer. Median age at diagnosis was 31.5 years (range: 22-35). Median AMH before treatment was 2.12 ng/mL (range 0.33-17.5) and dropped to 0.13 ng/mL (0.01-6.1, p < 0.0001) after a median delay of 387 days from diagnosis. A slight increase of 0.13 ng/mL to 0.30 ng/mL (0.01-3.2) was observed after more than 2 years of survey (p = 0.007 between 1 and 3 years AMH). No additional AMH increase was observed 5 years after the diagnosis in comparison to 3 years (n = 11).

Considering the median of age, AMH was not different in younger compared to older patients before or after treatment (1, 3, 5 years). For the whole population, the use of adjuvant hormonal therapy did not modify post-treatment AMH. In contrast, the post treatment median AMH was significantly lower after a 3FEC-3XT (n = 45, 83%) than after a FEC (n = 9, 17%) chemotherapy based regimen (0.09 and 0.38 ng/mL respectively, p = 0.01).

**Conclusions:** Despite a normal ovarian reserve before treatment, AMH decreases deeply 1 year after diagnosis, whatever the age of the patient. A slight recovery can be observed 3 years after diagnosis, without reaching the normal expected values for the age. Use of taxanes seems to increase gonadotoxicity.

Legal entity responsible for the study: Centre Henri Becquerel

Funding: Centre Henri Becquerel, Department of Biopathology

Disclosure: All authors have declared no conflicts of interest.

**Abstract 204P**

### Follow-up of chemotherapy induced changes in anti-Mullerian hormone, antral follicle number and ovary volume in premenopausal breast cancer patients


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**Background:** Ovarian functions in premenopausal breast cancer patients are frequently affected due to the applied chemotherapy regimen. In this study, we aimed to evaluate the ovarian functions after chemotherapy by assessing the AMH, the number of antral follicle and the volume of ovaries in the premenopausal patients with breast cancer.

**Methods:** Fifty-one premenopausal operable breast cancer patients who were given adjuvant and neoadjuvant chemotherapy were included in our study. We planned to evaluate the changes of serum AMH levels throughout the timeline of the study and ovarian volume-antral follicle numbers measured by transvaginal ultrasonography. First measurements were performed before chemotherapy and repeated in every 3 months for one year follow-up period.

**Results:** Interim third month and initial results of 31 patients were evaluated. Median age: 39 (range: 23-48). The results of 31 patients 3rd AMH results and the volume of ovaries in the premenopausal patients with breast cancer.

**Conclusions:** Despite a normal ovarian reserve before treatment, AMH decreases deeply 1 year after diagnosis, whatever the age of the patient. A slight recovery can be observed 3 years after diagnosis, without reaching the normal expected values for the age. Use of taxanes seems to increase gonadotoxicity.

Legal entity responsible for the study: Centre Henri Becquerel

Funding: Centre Henri Becquerel, Department of Biopathology

Disclosure: All authors have declared no conflicts of interest.

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<td><strong>Number of trials</strong></td>
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<td><strong>Number of patients</strong></td>
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<td><strong>% hormone receptors negative</strong></td>
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<td><strong>% taxane-alone</strong></td>
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<td><strong>APC/R overall</strong></td>
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<td><strong>p-interaction by type of chemotherapy</strong></td>
</tr>
<tr>
<td><strong>p-interaction by hormone receptors status</strong></td>
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<tr>
<td><strong>p-interaction by hormone receptors status versus others</strong></td>
</tr>
</tbody>
</table>

Funding: This meta-analysis was partially supported by AIRC (Associazione Italiana Ricerca Cancro)

Disclosure: All authors have declared no conflicts of interest.
Benefit from bevacizumab is needed.

Feasible, does not provide clinical benefit to patients with non-metastatic developed grade III bevacizumab-related toxicity (hypertension). One patient died of nausea and vomiting (5.8%), and febrile neutropenia (2.9%). Only one patient and bevacizumab (10 mg/kg) for 4 cycles followed by docetaxel (75 mg/m²) and

Between Oct, 2011, and Apr, 2015, we enrolled 34 patients, of whom 3 didn’t undergo surgery, leaving 31 patients in the primary endpoint analysis. After neoadjuvant therapy, 5 (16.1%) of 31 patients achieved a pathological complete response according to centralized review. One patient discontinued treatment due to adverse events. The most frequent grade 3–4 toxicities were neutropenia (23.5%), nausea and vomiting (5.8%), and febrile neutropenia (2.9%). Only one patient developed grade III bevacizumab-related toxicity (hypertension). One patient died of pneumonia after cycle 8 and before surgery, which was thought to be unrelated to bevacizumab. After 25.2 months of median follow-up (range: 2.3–43.3) five patients experienced a disease relapse (16.1%).

Conclusions: Our results seem to indicate that the addition of bevacizumab to dose-dense neoadjuvant chemotherapy with FEC and docetaxel, although safe and feasible, does not provide clinical benefit to patients with non-metastatic HER2-negative breast cancer. Translational research to identify patients who might benefit from bevacizumab is needed.

Background: Breast cancer is a leading cause of death in women worldwide. Neoadjuvant chemotherapy (NAC) is one of the treatment options for locally advanced breast cancer patients. Currently, there are no clinically useful predictive markers of response to NAC. We previously identified the chromosome regions in which copy number variations (CNVs) were correlated with response to NAC. Several studies have shown associations between drug effects and gene expression levels and specific mutations.

Methods: The criteria for inclusion in the study were as follows: luminal B breast cancer and clinical stage II or III disease. The study group consisted of 36 patients and the control group comprised 71 patients. The tissue samples were obtained with a biopsy prior to NAC. CNVs in biopsy specimens were tested using the high-density microarray platform. The expression levels of TMY3 and Top2α were determined by PCR. Depending on the molecular and genetic characteristics of the tumor, patients began treatment with NAC, docetaxel or FAC (fluorouracil, adriamycin, cyclophosphamide) or CAX (cyclophosphamide, adriamycin, capetitabine) or CP (cyclophosphamide, cisplatin) or AD (adriamycin, docetaxel) or surgery. All patients in the control group received NAC followed by surgery. Response to NAC was assessed by means of International Union Against Cancer criteria.

Results: Based on the findings of previous studies and literature data, we had developed an algorithm of personalized treatment with NAC for breast cancer patients. Patients having CNV markers of response to NAC (deletions in ABCB1, ABCG2, ABCG1, ABCB5, ABCB7) deletions in 19p11.1–32, 11q21–25 and amplification in 1q11–13 were treated with NAC. The choice of the NAC regimen depended on the Top2α amplification, deletions in BRCA1 and TUBB3, expression level of Top2α and TMY3. Of the 36 patients, 26 had markers of response to NAC and began treatment with NAC. Partial and complete response rate was 88.5% in the study group and 53.8% in the control group (p = 0.002).

Conclusions: The CNVs mentioned above could be considered as new markers of NAC response. The developed algorithm can be used for personalized treatment of breast cancer patients.

Legal entity responsible for the study: P. Kazantseva

Funding: Tomsk Cancer Research Institute, Tomsk, Russian Federation

Disclosure: All authors have declared no conflicts of interest.

Background: Addition of bevacizumab to standard chemotherapy in the neoadjuvant setting improves the proportion of patients with HER2-negative breast cancer who achieve pathological complete response. We aimed to assess the addition of bevacizumab to dose-dense neoadjuvant chemotherapy.

Methods: We enrolled women with operable HER2-negative breast cancer (T1c–T4 and N0–3). Patients underwent treatment every 2 weeks (with pegfilgrastim support) of fluorouracil (500 mg/m²), epirubicin (75 mg/m²), cyclophosphamide (500 mg/m²), and bevacizumab (10 mg/kg) for 4 cycles followed by docetaxel (75 mg/m²) and bevacizumab for 4 cycles. After surgery, patients received adjuvant radiotherapy, and hormone therapy (if indicated). The primary endpoint was pathological complete response in breast and the axilla, and safety of the combination. A two-stage trial design was planned with 15 and 33 patients to enroll, respectively. The trial was stopped early due to slow accrual and follow-up is ongoing.

Results: Between Oct, 2011, and Apr, 2015, we enrolled 34 patients, of whom 3 didn’t undergo surgery, leaving 31 patients in the primary endpoint analysis. After neoadjuvant therapy, 5 (16.1%) of 31 patients achieved a pathological complete response according to centralized review. One patient discontinued treatment due to adverse events. The most frequent grade 3–4 toxicities were neutropenia (23.5%), nausea and vomiting (5.8%), and febrile neutropenia (2.9%). Only one patient developed grade III bevacizumab-related toxicity (hypertension). One patient died of pneumonia after cycle 8 and before surgery, which was thought to be unrelated to bevacizumab. After 25.2 months of median follow-up (range: 2.3–43.3) five patients experienced a disease relapse (16.1%).

Conclusions: Interval carcinoma is a screen-detected tumor with a worse prognosis compared to Incident and prevalent carcinomas. Adjuvant CT did not modify survival in Prevalent and incident carcinomas. Therefore, the detection methods should be taken into account before administering adjuvant CT.

Legal entity responsible for the study: Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC)

Funding: Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC)

Disclosure: All authors have declared no conflicts of interest.

Background: Breast cancers (BC) detected by mammographic screening have shown to have better prognosis than symptomatic ones. The benefit of adjuvant chemotherapy (CT) in some localized BC is controversial, as it has potential side effects. The objective of this study is to analyze survival differences of adjuvant CT among screening BC.

Methods: This is a cohort study with 1,248 breast cancers included from 4 screening national programs, between 2,000–2006. Follow-up was ended in 2014. Risk of death was estimated through Cox analysis. Hazard Ratio was adjusted by chemotherapy group (with or without CT) and stage.

Results: Two hundred sixty six prevalent cases were diagnosed (41.7% with CT), 633 Incident (40.9% with CT), and 349 interval carcinomas (59.6% with CT). After a median follow-up of 102 months deaths were 22.1% for Interval, 10.4% for Incident and 7.9% for prevalent carcinomas. Prevalent and Incident carcinomas who did not receive CT had no differences in death risk with respect to those who received CT adjusting by the stage. However, comparing to Prevalent carcinomas without CT, Interval carcinomas have shown an increase risk of death more pronounced when CT is not administered (Table).

Table: 205P Risk of death was estimated through Cox analysis. *Hazard Ratio adjusted by chemotherapy groups (with or without CT) and stage

<table>
<thead>
<tr>
<th>Death Risk</th>
<th>HR</th>
<th>aHR**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening BC group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalent</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Incident</td>
<td>1.42 (0.87–2.34)</td>
<td>Ref</td>
</tr>
<tr>
<td>Interval</td>
<td>3.5 (2.15–5.7)</td>
<td>Ref</td>
</tr>
<tr>
<td>Group + CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalent without CT</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Prevalent with CT</td>
<td>0.54 (0.22–1.34)</td>
<td>1.72 (0.66–4.47)</td>
</tr>
<tr>
<td>Incident with CT</td>
<td>1.34 (0.67–2.67)</td>
<td>2.12 (0.92–4.89)</td>
</tr>
<tr>
<td>Incident without CT</td>
<td>0.91 (0.45–1.82)</td>
<td>1.82 (0.79–4.17)</td>
</tr>
<tr>
<td>Interval with CT</td>
<td>2.44 (1.25–4.77)</td>
<td>3.14 (1.37–7.17)</td>
</tr>
<tr>
<td>Interval without CT</td>
<td>3.5 (1.66–6.56)</td>
<td>3.69 (1.56–8.74)</td>
</tr>
</tbody>
</table>

Conclusions: Interval carcinoma is a screen-detected tumor with a worse prognosis compared to Incident and prevalent carcinomas. Adjuvant CT did not modify survival in Prevalent and incident carcinomas. Therefore, the detection methods should be taken into account before administering adjuvant CT.

Legal entity responsible for the study: Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC)

Funding: Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC)

Disclosure: All authors have declared no conflicts of interest.

Delayed initiation of HER2-targeted therapy (HER2Tx) is associated with a higher risk of relapse for early stage (ES) HER2-positive (HER2+) breast cancer (BrCa)

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Background: The prognosis of HER2+ ESBrCa has improved since the addition of trastuzumab (H) to chemotherapy (CRx). Several H/CRx regimens have been validated.
Results: We identified 592 pts treated between September 2001 and March 2013 and performed outcome analyses on 452 pts with a minimum of 36 months of follow up (FU). Pts characteristics: Neoadjuvant (Neoa) 95/Adjuvant (Adj) 357; N = 233 (52%); N = 211 (47%)/unknown = 8 (1%), ER = 282 (62%)/BR = 167 (37%)/unknown = 3. Therapy administered: TCH 251 (56%)/AC-TH 84 (19%)/ER = 167 (37%)/unknown = 3. Therapy timings: Administration of both H SC and H IV (range 5.5-169.6). The median time from BrCa Dx to first H is 11.9 weeks. Overall RFS rate is 80.5%. The relative risk of relapse for pts starting H ≥ 2 weeks from Dx is significantly increased with an HR 2.55 (95%CI 1.3-4.98 p = 0.006). This effect is particularly evident in pts with ER negative (p = 0.0069), node positive (p = 0.0197), and age <50yrs (p = 0.0036). On multivariate analysis initiation of H after 12 weeks, age <50 and positive nodal status were found independent prognostic factors of worse RFS.

Conclusions: These data suggest the possibility that the timing of initiation of H may be a determinant of outcome. Delay beyond 12 weeks increased the risk of relapse. Intriguingly, the very early administration of H, i.e. pre-operatively completely eliminated the negative prognostic effects of age and nodal status.

Legal entity responsible for the study: Medical Oncology Department St Vincent’s University Hospital

Funding: Medical Oncology Department St Vincent’s University Hospital

Disclosure: All authors have declared no conflicts of interest.

Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: final analysis of the randomised, two-cohort PrefHer study

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Background: PrefHer (NCT01401166) revealed a compelling and consistent patient preference for adjuvant subcutaneous trastuzumab (Herceptin® SC; H SC) over intravenous H (H IV) in HER2-positive early breast cancer, regardless of single-use injection device (Cohort 1) or hand-held syringe (Cohort 2) delivery. We report 3-year event-free survival (EFS) and safety.

Methods: Post-surgery and neo/ado (ado)adjuvant chemotherapy, patients were randomised to receive four adjuvant cycles of H SC (600 mg fixed dose) followed by four of H IV (8 mg/kg loading, 6 mg/kg maintenance doses), or vice versa every 3 weeks. Following this crossover period, patients continued H SC or H IV therapy to complete 18 standard cycles. H IV was allowed prior to randomisation. EFS was assessed using the Kaplan–Meier approach and is shown for the overall and intention-to-treat populations (patients who completed the primary preference question and 2.5% administration of both H SC and H IV in both cohorts combined. Adverse events (AEs) and serious AEs (SAEs) were reported according to NCI-CTCAE v4 and ICH E2A; data shown are combined from both cohorts (overall safety population) and include the crossover, H continuation and follow-up periods.

Results: Across 12 countries and 74 sites, 488 patients were randomised and 483 assessed for safety. The evaluable intention-to-treat population comprised 467 patients. Median follow up was 36.1 months (range 0.4–93.9). The 3-year EFS rate in the overall evaluable-intention-to-treat population was 90.6% (95% confidence interval 87.4–92.9). The AE profile is shown in the table.

Conclusions: EFS results confirm previous efficacy findings of H in the adjuvant setting. H SC was well tolerated and no new safety signals were identified compared with the known profiles of H IV or H SC from previous reports in HER2-positive early breast cancer.

Clinical trial identification: NCT01401166

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd

Funding: F. Hoffmann-La Roche Ltd

Disclosure: X. Pivot: Consultant with honorarium for Roche. Amgen, Novartis, Eisai, Pierre Fabre. S. Vermas: Advisory Board: Amgen, Astra Zeneca, BI, Novartis, Pfizer, Roche, Spectrum Health; Other: Medical Director and Co-Founder, OncologyEducation.com. L. Fallowfield: Grant support for the PrefHer study from Roche. V. Müller: Speaker honoraria from Roche and consultancy honoraria from Roche. Z. Machackova: Stock ownership (F. Hoffmann-La Roche). Other substantive relationships (employee of F. Hoffmann-La Roche). S. Osborn: Other substantive relationships (Employee of F. Hoffmann-La Roche). J. Gligorov: Consultancy. Roche-Genentech; Eisai: Honoraria; Teva; Novartis-GSK; GenomicHealth. All other authors have declared no conflicts of interest.

Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: final analysis of the randomised, two-cohort PrefHer study

1Chemotherapy – Oncology, CHU Jean Minjoz, Besançon, France, 2Ardèche Cancer Centre, University Hospital Coventry and Warwickshire, Coventry, UK, 3Department of Medical Oncology, Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain, 4Medical Oncology Department, APHP-Tenon; IUC-UPMC; Sorbonne University, Paris, France, 5Department of Medicine, Pontifical Catholic University of Rio Grande do Sul School of Medicine, Porto Alegre, Brazil, 6Clinic for Oncology and Radiotherapy, University Hospital Spät, Spät, Croatia, 7Medical Oncology, San Raffaele IRCCS, Milan, Italy, 8Department of Medical Oncology, Amphia Ziekenhuis, Breda, Netherlands, 9Global Product Development/Medical Affairs Oncology (PDMAO), F. Hoffmann-La Roche Ltd, Basel, Switzerland, 10PDMA Operations (Biometrics), F. Hoffmann-La Roche Ltd, Dein Heuwela, Austria, 11Department of Internal Medicine, Medical University of Vienna, Vienna, Austria

Background: Neoadjuvant–adjuvant subcutaneous trastuzumab (Herceptin® SC; H SC) is non-inferior to intravenous H (H IV) in terms of pathological complete response (pCR) in the breast for HER2-positive early breast cancer (EBC) (Jacksich, Lancet Oncol 2012). pCR/total pCR is associated with improved event-free survival in this setting, and H SC and H IV have comparable safety profiles (Jacksich, Lancet Oncol 2012; ASCO 2013). UmbHER1, a Phase IB, open-label, multinational, umbrella study aims to assess the safety and tolerability of H SC in a broader patient population, including those with EBC or metastatic BC (MBC) treated with or without chemotherapy (CT) or pertuzumab (PERJETA®). UmbHER1 is composed of five EBC and two MBC studies; we present pooled interim safety data from the five EBC studies.

Methods: The EBC UmbHER1 studies are: NCT01401497 (neoadjuvant–adjuvant H SC + CT; N = 228), NCT01926888 (neoadjuvant–adjuvant H IV + H SC; N = 102), NCT02194166 (adjuvant H IV + H SC; N = 90), NCT01964391 (neoadjuvant–adjuvant H SC + CT; N = 174), NCT02049095 (adjuvant H SC; N = 125). In all studies, H SC was administered as a 600 mg fixed dose and given every 3 weeks until progression/ unacceptable toxicity/withdrawal (18 cycles/1 year). The overall primary objective is safety and tolerability. Results are descriptive and include treatment cycles (H SC, H IV and CT).

Results: The EBC safety population comprises 719 patients. There were 8219 H SC cycles administered for EBC by data cut-off (27 November 2015). The overall adverse

Abstracts

Table: 209P

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Overall safety population N = 483</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>388 (80)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>360 (75)</td>
</tr>
<tr>
<td>2</td>
<td>214 (44)</td>
</tr>
<tr>
<td>3</td>
<td>45 (9)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>SAEs</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Related to study drugs</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Resolved without sequelae</td>
<td>18 (4)</td>
</tr>
</tbody>
</table>

*Could be counted once per grade but ≥ once overall
event (AE) profile in the EBC population is shown in the table. The most common grade 3–4 serious AE (SAE) was decreased ejection fraction (3 patients, all grade 3).

### Table: 210P

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Overall EBC population N = 719</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>588 (82)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>533 (74)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>344 (48)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>103 (14)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>18 (3)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>33 (5)</td>
</tr>
<tr>
<td>SAE</td>
<td>52 (7)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>18 (3)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>105 (15)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>91 (13)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (≤1)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
</tr>
</tbody>
</table>

**Adverse events (AEs) were graded 1–4 per NCI-CTCAE v4.0. Numbers are irrespective of relationships to H.**

### Conclusions:

No new safety signals were identified with H SC, administered with or without CT for HER2-positive EBC, in this broad UmbHER1 population.

### Clinical trial identification:

NCT01940497 NCT01926886 NCT02194166 NCT01964391 NCT02040935

### Legal entity responsible for the study:

F. Hoffmann-La Roche Ltd

### Funding:

F. Hoffmann-La Roche Ltd

### Disclosure:


### Adjuvant subcutaneous trastuzumab for HER2-positive early breast cancer: Phase III SafeHer study subgroup analyses of body weights, active medical conditions, safety and tolerability

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### Background:

The Phase III, non-randomised, multinational, open-label SafeHer study (NCT01566721) confirmed the safety and tolerability profile of 600 mg fixed-dose subcutaneous trastuzumab (Herceptin® SC [H SC]), administered every 3 weeks (qw) for 18 cycles/1 year from an H SC Vial via hand-held syringe or from a single-use injection device (SID), as adjuvant therapy for HER2-positive early breast cancer (Gilgore J, et al. EBCC 2016; P326). The safety and tolerability of H SC 600 mg fixed-dose therapy may be affected by patients’ body weights and active medical conditions, especially in patients with lower body weights. We assessed these factors in an exploratory analysis of SafeHer.

### Methods:

Adverse events (AEs) and serious AEs (SAEs) were recorded/graded per National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0. Congestive heart failure (CHF) was assessed by NCI-CTCAE v4.0 / New York Heart Association functional classification. Results are descriptive. Data are from the combined H SC Vial and H SC SID cohorts, from the first H SC dose until 28 days after the last dose (plus a 5-day window). SafeHer study follow-up will continue for 5 years.

### Results:

Safety and active medical conditions of interest by weight subgroup are shown in the table.

### Table: 211P

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Overall N = 2573</th>
<th>Very low weight ≤49 kg, n = 164</th>
<th>Low weight 50 kg – 77 kg, n = 204</th>
<th>Quartile 1, 1.53 kg ≤57 kg, n = 441</th>
<th>Quartile 2, 58 kg – 87 kg, n = 445</th>
<th>Quartile 3, 88 kg – 117 kg, n = 425</th>
<th>Quartile 4, 118 kg– 156 kg, n = 427</th>
<th>Quartile 5, 157 kg – 196 kg, n = 425</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 AE</td>
<td>228 (89%)</td>
<td>36 (22%)</td>
<td>185 (91%)</td>
<td>31 (7%)</td>
<td>35 (8%)</td>
<td>35 (8%)</td>
<td>35 (8%)</td>
<td>35 (8%)</td>
</tr>
<tr>
<td>Grade 3 AE</td>
<td>154 (62%)</td>
<td>8 (5%)</td>
<td>14 (8%)</td>
<td>29 (7%)</td>
<td>30 (7%)</td>
<td>31 (7%)</td>
<td>29 (7%)</td>
<td>29 (7%)</td>
</tr>
<tr>
<td>Grade 4 AE</td>
<td>14 (6%)</td>
<td>3 (2%)</td>
<td>2 (1%)</td>
<td>5 (1%)</td>
<td>5 (1%)</td>
<td>5 (1%)</td>
<td>5 (1%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>All AEs</td>
<td>366 (14%)</td>
<td>21 (13%)</td>
<td>21 (13%)</td>
<td>36 (9%)</td>
<td>37 (9%)</td>
<td>37 (9%)</td>
<td>37 (9%)</td>
<td>37 (9%)</td>
</tr>
</tbody>
</table>

### Conclusions:

In this SafeHer subgroup analysis, the safety results were comparable for the H SC 600 mg qw fixed dose among the lower-body-weight subgroups and the overall patient population. In the higher-body-weight subgroup, grade 2–3 AE and SAE rates were slightly higher than the overall patient population, which may be influenced by the higher rate of active medical conditions in the higher-body-weight subgroups; nevertheless, grade 2–3 and serious cardiac disorders remained comparable across all weight subgroups.

### Clinical trial identification:

NCT01566721

### Legal entity responsible for the study:

F. Hoffmann-La Roche Ltd

### Funding:

F. Hoffmann-La Roche Ltd

### Disclosure:

B. Ataseven: Membership of an advisory board (Roche). Other substantive relationships (honorarium for lectures: Roche, AstraZeneca; Travel expenses support: Roche). M. Verrill: Stock ownership (Roche, Novartis, Amgen, Pfizer). J. Gligorov: Consultancy: Roche-Genentech; Eisai Honoraria: Teva; Travel expenses support: Roche, Amgen, Novartis, Eisai, Pierre Fabre. M. De Laurentiis: Membership of an advisory board (Roche, Celgene, AstraZeneca, Novartis, Pfizer, Teva, Chugai); Corporate-sponsored research (Roche, Novartis, Amgen). X. Pivot: Consultant with honorarium for Roche, Amgen, Novartis, Eisai, Pierre Fabre. M. De Laurentis: Membership of an advisory board (Roche, Genentech, Novartis, Pfizer, Teva, Chugai). Corporate-sponsored research (Roche, Novartis, Amgen). H.A. Azim: Membership of an advisory board (Roche, Pfizer, Novartis & Amgen); Corporate-sponsored research (Bayer & Pfizer). All other authors have declared no conflicts of interest.

### 212P Fatigue and quality of life (QoL) during and after adjuvant treatment by trastuzumab (Herceptin®) among breast cancer patients (BC pts): a case-control study

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1Oncology Department, Centre Francois Baclesse, Caen, France, 2Clinical Research Department, Centre Francois Baclesse, Caen, France, 3Oncology Department, Centre Francois Baclesse, Caen, France, 4Radiotherapy Department, Centre Francois Baclesse, Caen, France

### Background:

Trastuzumab (Herceptin®, Roche) has become a mainstay in the treatment of pts with human epidermal growth factor receptor-2 (HER2)-overexpressing breast cancer in the adjuvant setting. Trastuzumab treatment consists in 21-day cycles during the last 3 cycles of FEC100-Doxetaxel chemotherapy (CT) and 15 additional cycles thereafter. Although adjuvant CT was shown to have a
deleterious effect on QoL and fatigue in BC pts, no data are available on experience of BC pts during this additional one-year treatment period by Trastuzumab. This case-control study assessed fatigue and QoL during and after Trastuzumab treatment as compared to age-matched BC pts receiving the same CT without Trastuzumab.

Methods: 70 pts were included (35 pts in each group) on day 1 of last cycle of CT (first day of Trastuzumab for case group). The primary endpoint was severe fatigue (FACT-F < 37) at 9 months (mo) post CT. QoL (FACT-G, Fact-B), fatigue (FACT-F) and anxiety/depression (HADS) were assessed at 3, 6, 9, 15 mo post CT.

Results: No statistically significant differences were noted at baseline between groups: age (48 ± 10 yr); marital status (87%); surgery (mastectomy, 42%); CT (all pts received complete FEC100-Docetaxel treatment except one pt who received only 1 cycle of Docetaxel, dose reduction for 12 pts); radiotherapy (84%); hormone therapy (69%); anxiety (41%); depression (23%); severe fatigue at baseline (66%). At 9 mo post CT, proportion of pts with severe fatigue (39%) did not statistically significantly differ between groups and a significant reduction of severe fatigue from baseline was noted (p < 0.0001). QoL and severe fatigue did not differ between groups over time.

Conclusions: Trastuzumab treatment was not shown to have a deleterious impact on fatigue and QoL in adjuvant setting as compared to CT with no indication to Trastuzumab treatment. CT-induced fatigue appears to improve similarly between women receiving or not Trastuzumab, despite a one-year longer duration of treatment.

Clinical trial identification: Clinical trial information: NCT01400438

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

214P Effect of polypharmacy on treatment preferences and outcome in older breast cancer patients

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Background: In older cancer patients, polypharmacy is at least as common as it is in individuals of the same age without cancer. However, information related to polypharmacy in older cancer patients is limited. The aim of this study is to evaluate the prevalence of polypharmacy in older breast cancer patients at the time of diagnosis and its association with treatment preferences and disease outcome.

Methods: A total of 418 breast cancer patients who were 65 and older at the time of diagnosis between 2001 and 2014 were retrospectively analyzed. Polypharmacy has been defined according to the number of drugs that an individual takes or to the risk of at least one severe drug interaction. Patients were considered as polypharmacy (Arm A, n = 84) and non-polypharmacy group (Arm B, n = 334). Kaplan-Meier survival analysis was carried out for disease free survival (DFS) and overall survival (OS). Two-sided P values of <0.05 were considered statistically significant.

Results: The median follow-up time for this analysis was 37.5 months. Patient’s clinical and pathological characteristics are well-balanced between two arms. In patients with polypharmacy five year DFS rate was 63.5% whereas in patients without polypharmacy DFS rate was 67.9% (P = 0.699). Five-year overall survival rate in Arm A was 68%, while in Arm B was 75.7% (P = 0.249). The association between polypharmacy and disease outcome was also evaluated in “very old” breast cancer patients who are 80 years and older. In patients with polypharmacy three year DFS rate was 56.1% whereas in patients without polypharmacy, DFS rate was 88.2% (P = 0.031). Three-year overall survival rate was 88.2% and 64.5%, respectively (P = 0.105).

Conclusions: The prognostic effect of polypharmacy which is a common geriatric problem on survival has been evaluated in older breast cancer patients. The association between polypharmacy and DFS was found significant in patients 80 years and older. We believe our study contribute the ongoing research by showing the predictive effect of polypharmacy in very old breast cancer patients

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

215P The prognostic effect of chemotherapy in male breast cancer: An experience of 136 cases from a retrospective study

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Background: Male breast cancer (MBC) is a rare tumor. There were few researches concerning the effect of chemotherapy for MBC. The purpose of this study is to estimate the value of chemotherapy on prognosis in MBC.

Methods: From Jan 1990 to Jan 2008, the clinical and pathological materials of MBCs were collected and reconfirmed in Zhejiang Cancer Hospital in China. The disease-free survival (DFS) and overall survival (OS) between chemotherapy group and non-chemotherapy group were compared by Kaplan-Meier survival curve (Log-Rank). All survival factors were verified by COX proportional hazards model.

Results: The median follow-up time was 125 months (74 – 189 months). There were 26 cases (19.12%) with recurrence or metastasis in the follow-up time. Among those patients, 11 cases with bone metastasis (42.31%), 5 cases with multiple lesion-metastasis (19.23%), 3 patients with liver recurrent (11.54%), 3 cases with lung recurrent (11.54%), 2 cases with brain metastasis (7.69%) and 2 case with local recurrence (7.69%). The 10-year OS rate of all 136 patients was 71.80%. There were 20 cases (25%) with recurrence or metastasis in patients with chemotherapy, while 6 cases (10.70%) with recurrence or metastasis in patients without chemotherapy. The mean DFS time of MBC with chemotherapy and non-chemotherapy was 155.59 ± 7.68 months vs 154.31 ± 4.95 months, respectively, which could not achieve a significant difference (Log-Rank test, χ² = 3.645, P = 0.056). The mean OS time of MBC with chemotherapy and non-chemotherapy was 155.59 ± 7.68 months vs 154.31 ± 4.95 months, respectively (Log-Rank test, χ² = 2.469, P = 0.05). COX proportional hazard regression model indicated that chemotherapy did not have significant correlation with DFS (hazard ratio, HR = 0.371, p = 0.05), while it might be a protective factor on OS (HR = 0.108, p = 0.030), which appeared a high consistency with poor-prognosis factors such as histological grade, HR, HER2 and Ki67. The stratified analysis showed that MBC with positive lymph node and high histological grade have benefited from chemotherapy.

Conclusions: The utility of chemotherapy should be considered in the high-risk level of recurrence/metastasis in MBC.

Legal entity responsible for the study: Zhejiang Cancer Hospital

Disclosure: All authors have declared no conflicts of interest.
The impact of delay in adjuvant radiotherapy in the combined modality treatment of early stage breast cancer: single institutional experience

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Background: To study how the timing of radiation influences local control, disease-free survival (DFS) and overall survival (OS) in patients being treated with chemotherapy and radiation for early stage carcinoma of the breast.

Methods: In this retrospective study the medical records of patients who received adjuvant chemotherapy and radiotherapy (RT) for early stage breast cancer (I-II) after definitive surgery at the department of Clinical Oncology, Ain Shams University Hospitals were collected and reviewed.

Results: Between 2007 and 2009, 118 patients were collected and included for analysis. Patients were divided into 2 groups: Group A consisted of 56 patients that started adjuvant RT < 6 months after surgery and group B included 62 patients who had RT delay ≥ 6 months. Both groups were matched demographically. Comparisons of local control, overall survival and disease-free survival between group A and group B patients all revealed a significant difference in favor of group A. At 5 years, the local recurrence rate was 8.8% vs 17.2% (p = 0.01), OS rates were 96% vs 78 % (p = 0.01), while DFS rates were 86% vs 64% (p = 0.01). Analysis of other prognostic factors; age, tumour size, lymph node status, grade, HER2 status, type of surgery (modified radical mastectomy vs breast conserving surgery), chemotherapy regimen and local radiotherapy received were analyzed. Larger tumor size >2 and lymph node positive disease predicted for worse DFS (p = 0.05) and OS (p = 0.06).

Conclusions: In patients requiring chemotherapy and radiation treatments for early stage breast cancer, a delay in the initiation of radiation for a period exceeding 6 months from diagnosis resulted in a higher local failure rate. Furthermore, this higher local failure rate was associated with an increased rate of distant metastases and a reduced overall survival rate.

Legal entity responsible for the study: Ain Shams University

Funding: Ain Shams University

Disclosure: All authors have declared no conflicts of interest.

Concurrent paclitaxel and radiotherapy for node positive breast cancer

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Background: Concurrent chemo-radiotherapy in breast cancer (BC) may yield better local control with minimal toxicity in node positive patients. The feasibility of paclitaxel with radiotherapy was assessed for tolerability, cosmetic outcome as well as local control.

Methods: All female BC with stage II-III were included in the study. Adjuvant chemotherapy was 4 cycles AC (Doxorubicin 60mg/m2 + cyclophosphamide 600mg/m2) followed by 4cycles of Paclitaxel 60mg/m2 weekly for 12 weeks concurrent with 3D Conformal radiotherapy in a dose of 45Gy/20/4wks to the whole breast and supraclevicular nodal region. Boost of 10Gy/4fr was given to the tumor bed in conservative cases. Evaluation of lung function was done by carbon monoxide diffusion. Radiotherapy toxicity and breast cosmesis were assessed by the KTOG and Harvard criteria respectively. The cosmesis was assessed and scored at the beginning & end of RT and every 6 months thereafter. This was done by patient (subjective score) and physician (objective score) by comparing it with the contralateral untreated breast.

Results: There were 40 patients, 96% underwent modified radical mastectomy and the other half had conservative surgery. The mean age was 50 years (31-70). With 24months follow up, the overall survival was 92% with no local relapse or radiation pneumonitis. There was no significant change in carbon monoxide diffusion after radiotherapy in the operated breast. The local control rate was <10% and the distant control rate was 97.5%. The cosmesis was assessed and scored at the beginning & end of RT and every 6 months thereafter. This was done by patient (subjective score) and physician (objective score) by comparing it with the contralateral untreated breast.

Conclusions: In conclusion, concurrent chemo-radiotherapy with weekly paclitaxel minimized the treatment duration with acceptable tolerance, cosmesis and good local control.

Legal entity responsible for the study: Kasr Alainy Center of Oncology and Nuclear Medicine

Funding: Kasr Alainy Center of Oncology and Nuclear Medicine

Disclosure: All authors have declared no conflicts of interest.

Outcomes for radiation associated angiosarcoma of the breast

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Background: Angiosarcoma is a rare late effect of radiotherapy following early breast cancer treatment. This study looked at the management and outcomes for radiation associated angiosarcoma at our Cancer centre serving a population of 2.5 million

Methods: All patients diagnosed with breast angiosarcoma from Jan 1997- March 2016 were identified from electronic medical records. 41 patients were identified. 5 patients had primary angiosarcoma and were excluded. 36 had prior adjuvant radiotherapy for breast cancer and formed the study cohort. All patients were discussed by the central Sarcoma multidisciplinary team for pathology review and management planning.

Patient demographics, breast cancer treatment, radiotherapy details, date of diagnosis of radiation associated angiosarcoma (RAS) and surgical treatment details and pathological parameters of RAS including grade, size and margin information was collated. Date of recurrence and date of death were collected. Excel spreadsheet and SPSS were used to analyse the data.

Results: Median follow up was 5 years (Range 0.2-18 years). Median age at diagnosis was 70 years (Range 37-85). 32 patients had wide excision and 4 mastectomy for breast cancer. All had whole breast radiotherapy – 40 Gray in 15 fractions and 7 had additional breast boost radiation to tumour bed. Median time from radiotherapy to developing angiosarcoma was 7 years (Range 2 - 17). 32 patients had surgery for RAS with radical intent. 18 had clear (>10mm) and 10 patients had close margins(<10mm). 4 had unknown margins. The median OS for wide excision of tumor was 35 months with half the patients still alive. 19 patients had relapsed of which 15 had local recurrence. Local recurrence free interval was 11.4 months. Median time to relapse was 6.6 months if margins were <10mm vs 19.1months if clear margins.

Conclusions: RAS is a very rare late effect of radiation therapy with only 36 cases found over 20 years within a large population of 2.5 million. Latency for RAS can be shorter in some cases than widely recognised. It has a poor prognosis with median survival less than 3 years. Early detection and radical surgery with wide margins gives the best outcome.

Legal entity responsible for the study: Joji Joseph

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Window study of the PARP inhibitor rucaparib in patients with primary triple negative or BRCA1/2 related breast cancer (RIO)

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Background: Triple negative breast cancer (TNBC) constitutes 10-15% of breast cancers and currently no effective targeted treatments exist to improve outcome. PARP inhibitors are effective in germline BRCA (gBRCA) (gBRCA) mutated breast cancer due to defects in homologous recombination within sporadic TNBC subgroups could enhance responsiveness to PARP inhibition. However, trials have failed to show favourable responses with PARP inhibitors in heavily pre-treated advanced TNBC. RIO aims to determine the proportion of sporadic TNBCs that display sensitivity to the PARP inhibitor rucaparib and establish biomarkers that distinguish this subgroup, enabling identification of patients likely to benefit from rucaparib treatment.

Trial design: RIO is a single-group, open-label, phase II window of opportunity study assessing rucaparib efficacy in patients prior to commencing primary treatment. 81 primary, sporadic TNBC and up to 20 known gBRCA mutated patients will be recruited. Patients receive 12-14 days of rucaparib with core biopsies and research bloods collected pre- and post-treatment. Follow-up is 28 days post end of trial (EOxT). Baseline biopsies are collected at time of diagnostic biopsy or following trial entry. EOxT biopsies are taken during surgery or prior to neo-adjuvant chemotherapy. The primary endpoint is Ki67 response from baseline to end of rucaparib treatment in sporadic TNBC. Response is defined as ≥ 50% fall in Ki67 from baseline. Secondary and exploratory endpoints aim to define biomarkers associated with rucaparib responsiveness and surrogate markers of efficacy. The first patient was enrolled in August 2015. The trial is being conducted in the UK with 12-14 participating centres anticipated. The study is open to new centres with recruitment expected to complete early 2017. The RIO trial will allow biological effects of rucaparib in a treatment naive TNBC population to be assessed, enhancing biological understanding of TNBC subgroups. If successful, the results will inform future studies in targeted treatment options available for TNBC patients.

Clinical trial identification: ISRCTN 92154110 CRUK/12/034

Legal entity responsible for the study: Joji Joseph

Disclosure: None

References: All authors have declared no conflicts of interest.

Notes: None

Legal entity responsible for the study: The Institute of Cancer Research. Royal Cancer Hospital (ICR) and The Royal Marsden NHS Foundation Trust
Background: TNBC treated using neoadjuvant chemotherapy (NACT) has a varied prognosis with 50% of patients (pts) having excellent response to treatment (pCR/RCB-I) and excellent prognosis, while 50% have marked residual disease (RCB-II-III) and significantly worse prognosis. Lack of response to an initial NACT regimen also indicates a low chance (5%) of achieving pCR with subsequent chemotherapy, even if drugs are changed.

Trial design: This randomized study will determine the impact of predicting chemosensitivity to NACT using molecular characterization combined with diagnostic imaging and determine if offering a clinical trial of selected targeted therapy will impact outcomes (as measured by pCR and RCB-I) and excellent prognosis, while 50% have marked residual disease (RCB-II-III) and significantly worse prognosis. Lack of response to an initial NACT regimen also indicates a low chance (5%) of achieving pCR with subsequent chemotherapy, even if drugs are changed.

Clinical trial identification: ClinicalTrials.gov Identifier: NCT02276443 (10/21/2014)

Legal entity responsible for the study: MD Anderson

Funding: AstraZeneca

Disclosure: All authors have declared no conflicts of interest.
breast cancer, locally advanced and metastatic

**BOLERO-4: Phase 2 trial of first-line everolimus (EVE) plus letrozole (LET) in estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (BC)**

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**Background:** Efficacy of EVE + exemestane (EXE) in postmenopausal patients (pts) with hormone receptor-positive, HER2-advanced BC progressing on endocrine therapy was established in the phase 3 BOLERO-2 trial (statistically significant 4.6-month increase in median progression-free survival [PFS]; local assessment vs placebo + EXE). BOLERO-4 (NCT01698918) is the first trial to evaluate first-line EVE + LET efficacy and safety in postmenopausal pts with ER +, HER2-metastatic or locally advanced BC. Efficacy of EVE + EXE upon disease progression and a stomatitis therapeutic intervention are secondary objectives.

**Methods:** Postmenopausal pts with ER +, HER2-metastatic or locally advanced BC with no prior advanced disease therapy received EVE 10 mg/day + LET 2.5 mg/day until further progression or unacceptable toxicity. Pts with stomatitis completed the Oral Stomatitis Daily Questionnaire and were randomized to local standard of care or alcohol-free saline rinse, where commercially available. Primary endpoint: PFS (first-line setting; local assessment), secondary endpoints: overall response (ORR), clinical benefit (CBR) rate, overall survival (OS), safety (first and second line), and change in stomatitis severity and duration.

**Results:** Best overall response n = 51 evaluable pts (median age, 64 years) in 13 countries participated: 194 pts (96%) with metastatic BC and 8 pts (4%) with locally advanced BC. 93 (46%) and 87 (43%) pts received prior hormonal therapy and chemotherapy (neo-/adjuvant setting). The median duration of follow-up was 17.5 months. The median PFS was not yet reached at data cutoff (12 months after the last patient’s visit). The estimated PFS rates (95% CI) were 83.6% (77.3-88.2%) and 71.4% (64.0-77.7%) at 6 and 12 months, respectively. ORR and CRR were 42.6% (35.5-49.7%) and 74.3% (67.7-80.1%), respectively. The most common adverse events were stomatitis (67.8%), weight loss (42.6%), and diarrhea (36.1%).

**Conclusions:** EVE combined with LET is an effective regimen in HR +, HER2-advanced BC in the first-line setting.

**Clinical trial identification:** CRAD001Y24135 Release date: 10 Aug 2015

**Legal entity responsible for the study:** Novartis Pharmaceuticals Corporation

**Funding:** Novartis Pharmaceuticals Corporation

**Disclosure:** M. Royce: Research funding from Novartis and Amgen. C. Villanueva: A consulting or advisory role with Roche, Novartis and Genentech. T. Bachet: Membership on the board for Roche, Novartis, Zeneca and Pfizer; research funding from Roche and Novartis; speaker fees from Novartis. C. Mariks: Employment: Employment with Novartis Pharma S.A.S. J. Lin: Discloses employment with Novartis Pharmaceuticals Corporation. F. Ringeisen: Employment and stock ownership in Novartis Pharma AG. F. Cardoso: Honoraria from AstraZeneca, Genentech, MerckSharp, Merus BV, Novartis, Pfizer, PierreFabre, Roche, Sanofi, Teva. All other authors have declared no conflicts of interest.

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**Anti-tumor activity of PM01183 (lurbinectedin) in BRCA1/2-associated metastatic breast cancer patients: results of a single-agent phase II trial**


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4Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA
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**Background:** PM01183 (lurbinectedin) is a new anticancer drug that blocks trans-activated transcription, induces DNA double-strand breaks and modulates the tumor microenvironment. PM01183 activity has been observed in different tumor types, and in patients resistant to platinum-based chemotherapy (CT). The activity observed against homologous-recombination-deficient cell lines prompted a phase II trial in metastatic breast cancer (MBC) patients (pts) with deleterious germline BRCA mutations (BRCA+).

**Methods:** BRCA+ MBC pts pretreated with ≥3 CT regimens in the advanced/metastatic setting, measurable disease per RECIST v1.1, performance status (PS) ≤1, and adequate major organ function were treated with PM01183 IV qwk. A protocol amendment adjusted the starting dose from 7 mg fixed dose (FD) to 3.5 mg/m2 to improve safety. Primary endpoint was overall response rate (ORR) by RECIST v1.1 with further development of PM01183 if ≥17 responses of 53 evaluable pts were confirmed.

**Results:** As of May 2016, 54 eligible pts (median age 43 years, median 1 prior advanced CT) have been treated (35 with 7 mg FD, 19 with 3.5 mg/m2). PS 0: 30 pts; prior anthracyclines: 45 pts, taxanes: 47 pts, platinum: 27 pts, PARP inhibitors: 9 pts; >2 metastatic sites: 33, BRCA 1: 30 pts; triple negative: 31 pts.

**Table 2230**

<table>
<thead>
<tr>
<th>Median cycles (range)</th>
<th>4 (1–24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td>n = 51 evaluable</td>
</tr>
<tr>
<td>CR</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>PR</td>
<td>19 (37%)</td>
</tr>
<tr>
<td>SD</td>
<td>22 (43%)</td>
</tr>
<tr>
<td>PD</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>ORR (95%CI)</td>
<td>39% (26–54) / 37 / 44% (7 mg FD / 3.5 mg/m2)</td>
</tr>
<tr>
<td>Platinum pretreated</td>
<td>23% (9–44)</td>
</tr>
<tr>
<td>Median duration of response (months) (95%CI)</td>
<td>4.6 (3.4–11.3)</td>
</tr>
<tr>
<td>Progression-free survival (months) (95%CI)</td>
<td>4.1 + (2.6–6.0)</td>
</tr>
</tbody>
</table>

Most common grade (G) 3–4 related adverse events (7 mg FD / 3.5 mg/m2) were: neutropenia 71 / 50 (G4 / G5); febrile neutropenia 29 / 6; thrombocytopenia 26 / 6 (G4 / G6, 2010); G3 fatigue 17 / 17; transaminase increase 26 / 11 (G4 / G3, 0); and G3 nausea 9 / 6. **Conclusions:** Primary endpoint was met. PM01183 is an active drug in BRCA+ MBC, regardless of prior platinum treatment. At 3.5 mg/m2, the tolerability improved notably, while maintaining the efficacy. Further development is warranted in this indication and a Phase 3 trial is planned.

**Clinical trial identification:** NCT01525589

**Legal entity responsible for the study:** PharmaMar S.A.

**Funding:** PharmaMar S.A.


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**Efficacy and safety of BCD-022, trastuzumab biosimilar candidate, compared to herceptin: Results of international multicenter randomized double blind study in patients with HER2+ mBC**

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**Background:** BCD-022 demonstrated equivalence to Herceptin in a comprehensive comparability physicochemical, non-clinical PK and PD studies, as well as phase I PK studies in patients with HER2+ mBC.

**Methods:** 126 patients with HER2-positive metastatic BC were randomly assigned into 2 groups at a ratio of 1:1 to receive BCD-022 or Herceptin at a loading dose of 8 mg/kg and then in maintenance dosage of 6 mg/kg in combination with paclitaxel (175 mg/m²) every 3 weeks up to 6 cycles of therapy or until progression or unbearable toxicity.

**Results:** ORR (primary endpoint) in both groups had no statistically significant differences: 53.57% (CI 40.70 to 65.98%) in BCD-022 group and 53.76% (CI 40.67 to 66.31%) in Herceptin group. The lower limit of 95% CI for ORR difference between the groups (-19.83%) did not exceed the non-inferiority margin, hence BCD-022 is non-inferior to Herceptin. There were also no differences between the groups for all other efficacy parameters: CR (73.02 vs 73.77%), anemia (82.4% vs 77.05%), leucopenia (73.02 vs 68.85%), thrombocytopenia (46.57 vs 49.94%), ALP increase (38.68 vs 42.62%), AST increase (42.86 vs 46.26%), ALT increase (33.33 vs 40.8%), diabetes (53.33 vs 43.49%), arthralgia (17.46 vs 18.03%), etc. Cardiovascular events specific for trastuzumab included: tachycardia (34.92 vs 20.98%), alopecia (33.33 vs 34.43%), arthralgia (17.46 vs 18.03%) etc. Cardiovascular events specific for trastuzumab included: tachycardia (34.92 vs 20.98%), alopecia (33.33 vs 34.43%), arthralgia (17.46 vs 18.03%) etc.

**Conclusion:** BCD-022 demonstrated non-inferiority to Herceptin in patients with HER2+ mBC.

**Clinical trial identification:** NCT01740422

**Legal entity responsible for the study:** JSC "BIOCAD"

**Funding:** JSC "BIOCAD"

**Disclosure:** All authors have declared no conflicts of interest.

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**First line endocrine therapy versus chemotherapy for HR+/HER2- metastatic breast cancer in the phase III STIC trial: clinical choice and validity of CTC count**

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**Background:** In patients (pts) diagnosed with HR+/HER2- metastatic BC the choice between front-line hormone therapy (HT, favored option) or chemotherapy (CT) is based on prognostic factors that are overpassed by CTC count. The STIC CTC trial is a large multicentric phase III randomized trial comparing two strategies to choose the front-line treatment type: decision by clinician vs by CTC levels.

**Methods:** Clinical/pathological characteristics were registered at time of inclusion, together with the a priori treatment preferred by clinicians (HT or CT). CTC count was then performed by Cellsearch® and pts were randomized between a priori treatment and CTC-driven treatment (HT if <5 CTC/7.5ml; CT otherwise). In addition to usual tests, we used multiple correspondence analysis (MCA) to detect and represent underlying structures in our dataset.

**Results:** This analysis was performed on 530 randomized pts. Main adverse prognostic factors were PS = 2 or 3 (7%), liver (20%) or pleuropulmonary (37%) metastases, >= 3 factors were PS = 2 or 3 (7%), liver (20%) or pleuropulmonary (37%) metastases, >= 3 metastatic sites (34%), lymphocytopenia (39%). HT was the a priori treatment for 371

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**Methodology:** PALOMA-2 randomized patients 2:1 to palbociclib + letrozole (N=444) or placebo + letrozole (N=222). Patient reported outcomes were assessed at baseline, day 1 of cycle 2, 3 and day 1 of every other cycle from cycle 5 until end of treatment using the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire. FACT-B includes FACT- General (FACT-G) and BC-specific subscale (BCS). FACT-B produces five subscale scores: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EBW), functional wellbeing (FWB), and a BC subscale (BCS), used to derive overall FACT-B, FACT-G, and Trial Outcome Index (TOI). Scores. A higher score indicates a better QOL. Repeated measures mixed-effects analyses were performed to compare between treatments change from baseline in each subscale and FACT-B scores, controlling for baseline.

**Results:** Baseline scores were comparable between the two treatment arms for FACT-B (102 vs 103), FACT-G, TOI and each of the subscale scores. There were no significant differences between the treatment groups in change from baseline scores for PWB (0.3 vs. -0.3, p = 0.414), SWB (0.6 vs -0.7, p = 0.762), EBW (0.7 vs 0.5, p = 0.386) and FWB (0.2 vs 0.3, p = 0.707). Overall change from baseline scores was comparable for the BCS (0.19 vs 0.83, p = 0.055), Trial Outcome Index (-0.1 vs 0.71, p = 0.325), FACT-G (-0.19 vs. 0.51, p = 0.882) and FACT-B (-0.11 vs 0.22, p = 0.782).

**Conclusions:** The addition of palbociclib to letrozole maintains HRQOL in treatment naïve postmenopausal patients with ER+ HER2- MBC and showed no significant difference compared to letrozole alone. This data adds favorably to the significant improvement in PFS seen in PALOMA-2.

**Clinical trial identification:** Pfizer: NCT01740427

**Legal entity responsible for the study:** Pfizer, Inc

**Funding:** Pfizer, Inc

**Disclosure:** H. Rugo: Institution receives research funding from Pfizer, Novartis, Lilly. V. Dieras: Consultant/Advisory role – Roche, Pfizer, Novartis Speaker's Bureau - Roche, Pfizer, Novartis. R. Finn: Consultant/Advisory role – Pfizer, Bayer, Novartis, Bristol Myers Squibb Institution receives research funding from Pfizer.D. Slamon: Stock Ownership; Travel Accommodations or Expenses – Pfizer. N. Harbeck: Honoraria – Astra Zeneca, Roche/Genetech, Novartis, Puma. N. Harbeck: Honoraria– Amgen, Celgene, NanoString Technologies, Novartis, Pfizer, Roche. Consultant/Advisory Role – AstraZeneca, Celgene, Genomic Health, Novartis, Roche/Genentech, Sandoz, Web, Research Funding. Boehringer Ingelheim: Novartis, Pfizer, Roche/Genentech, Sandon. All other authors have declared no conflicts of interest.
Background: Everolimus in an mTOR inhibitor that is approved to be in use in combination with exemestane for the treatment of postmenopausal patients with hormone receptor positive metastatic breast cancer. In this study we evaluate the patterns of care and complications associated with the use of this medication.

Methods: Breast cancer patients treated with everolimus between 2009-2014 were identified in the MarketScan database, a nationwide, employment-based database that includes claim data of employees and their dependents. The everolimus treatment pattern was evaluated. The frequency of toxicities as well as associated emergency room (ER) visits and hospitalizations between the first claim and 30 days after the last claim for everolimus were identified. Descriptive statistics were used.

Results: In all, 2949 everolimus-treated breast cancer patients were identified; the median age was 60 years old. The median of cumulative days of supply was 112 days, at the time of the first claim the initial prescribed dose was 10mg in 76.9% of the patients, 2.7% received a dose of 7.5mg, 17.8% 5mg and 2.6% received a 2.5mg prescription. Compared to the initial dose, 77.3% of the patients maintained the same dose, 16.7% decreased it and 6% increased it. A total of 1488 patients (50.9%) had claims associated with known everolimus-related toxicities; nausea, vomiting and electrolyte imbalances were identified in 31.7% of the patients, 17.9% had metabolic toxicities, 11.9% hematological toxicities, 5.1% stomatitis, 4.7% rash and 0.4% had a claim for pneumonitis. A total of 644 patients (21.8%) were hospitalized or had an ER visit associated with the toxicities above.

Conclusions: Half of the patients receiving everolimus had a claim for a known everolimus-related toxicity and 21.8% were hospitalized or visited the ER while on everolimus for a toxicity. We cannot rule out that symptoms that lead to the hospitalization/ER visit were not related to the breast cancer or to other cancer; but this data provides real world information of the toxicities associated with everolimus treatment. The pattern of toxicities differs from what has been reported in clinical trials, it is possible that only serious toxicities are associated with a claim.

Legal entity responsible for the study: The University of Texas MD Anderson Cancer Center

Funding: Susan G. Komen, The Duncan Family Institute, CIPRIT

Disclosure: M. Chavez-Macgregor, I have received research support form Novartis (institutional). I have served as a Consultant for Pfizer and Roche. All other authors have declared no conflicts of interest.

BRAF genomic alterations in breast cancer

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Background: Targeting BRAF genomic alterations (GA) in non-melanoma cancer patients is well-established, but BRAF targeting for treating metastatic breast cancer (mBC) remains under investigation.

Methods: DNA was extracted from 40 microns of FFPE sections of 7850 tumors, and comprehensive genomic profiling (CGP) was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 579X for up to 315 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. Genomic alterations (GA) included base substitutions (sub), indels, copy number alterations (CNA), fusions, chromosomal rearrangements.

Results: A total of 83 (1.1%) cases of BRAF altered BC were identified. The mean age of the 83 patients was 57 years (range 32 to 84 years). The primary tumor was used for CGP in 29 (34.9%) cases and from metastatic sites including lymph nodes, liver, bone, lung, brain adrenal and soft tissue in 54 (65.1%). Of these 83 tumors, there were 39 ductal, 1 inflammatory, 3 metastatic, 2 lobular and 38 NOS mBC. BRAF GA that may lead to aberrant MAPK signaling included amplifications (51.8%), V600E sub (15.7%), V600E sub (3.6%), other missense sub (21.6%), and fusions (6.0%); 5 additional mutations are uncharacterized for their effect on BRAF signaling activity (3.6%). The identified alterations were KIAA1549-BRAF (2), AGK-BRAF (1), FCHSD2-BRAF (1), and KLHDC10-BRAF (1). There was a statistically significant reduction in ERBB2 mutations in tumors harboring a BRAF GA (amplification or sub)/p (0.011). Of the cases harboring BRAF GA, 38.6% were TNBC, 21.7% HR+/HER2-, 2.4% HR+/HER2+, 2.4% HR+/HER2+ and 30.3% status unknown. Targetable genes more commonly amplified in tumors with BRAF GA, compared to BRAF WT breast cancer, include CDK6 (p < 0.001), HGF (p < 0.001) and MET (p < 0.001).

Conclusions: BRAF GA are uncommon in BC, identified in 1.1% of cases, but include targetable base substitutions and rare fusions. BRAF GA in mBC appear to be more common in HER2 negative and TNBC mBC, and there is a significant decrease in ERBB2 mutation in tumors with BRAF GA. Targetable genes co-altered with BRAF in BC include CDK6, HGF and MET. Further study of BRAF alterations in BC was warranted.

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Foundation Medicine, Inc.

Disclosure: J.A. Elvin, J. Suh, J-A. Vergilio, S. Ali, V. Miller, P. Stephens, L.M. Gay, J.S. Ross: Employee of and stockholder in Foundation Medicine, Inc. All other authors have declared no conflicts of interest.

Comprehensive genomic profiling of 9,654 breast carcinoma reveals therapeutically targetable molecular subtypes beyond those defined by hormone-receptor expression

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Background: Breast carcinomas (BC) are commonly classified into 4 subtypes based on hormone receptor expression: basal, luminal A, luminal B, and HER2 overexpressed. Comprehensive genomic profiling (CGP) can reveal targetable genomic alterations (GA) and redefine BC classification into therapeutically relevant subtypes.

Methods: DNA was extracted from 40 microns of FFPE sections for 8654 consecutive BCs. CGP was performed on hybridization-captured, adaptor ligation-based libraries (mean coverage >300X) for up to 315 cancer-related genes. Total mutational burden (TMB) was determined on 1.2 Mbp of sequenced DNA. Clinically relevant GA (CRGA) are GA linked to drugs on the market or under evaluation in clinical trials. Immunotherapy (IO) sensitivity is defined as TMB ≥ 20 mut/Mbp or mutation of specific DNA repair pathways. Homologous recombination (HR) deficiency is defined as mutation of the BRCA genes, other genes in the FANC complex, or DNA repair genes that have been shown to confer sensitivity to PARP inhibitors.

Results: Several distinct pathways are altered in BC, and these pathways are targetable with therapies that are FDA approved for oncology indications. Rare mutations can also be found in targetable kinases such as RET, ROS1, and RAF. 6959 (80.4%) tumors harbor a GA in at least one pathway, and 2697 (31.2%) BC harbor alterations in just one pathway (unique cases). Only 9.8% of BC would be HER2-positive by IHC.

Conclusions: CGP can identify CRGA that can stratify tumors by predicted sensitivity to a variety of therapies, including HER2- or mTOR-targeted therapies, immunotherapies, and other kinase inhibitors. 80% of BC harbor targetable GA, and 30% of samples harbor mutations in only one pathway. Many GA would not be identified by IHC or hotspot testing, but can be detected by next-generation sequencing. CGP is a powerful tool for guiding treatment across therapeutically distinct, but targetable, pathways.

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Foundation Medicine, Inc.

### Table: 229PD

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<th>IO sensitive</th>
<th>PKD/AKT/mTOR pathway</th>
<th>FGFR pathway</th>
<th>CDK pathway</th>
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</tbody>
</table>

#### 229PD

**Phase II randomised clinical study of metformin plus chemotherapy vs chemotherapy alone in HER2 negative metastatic breast cancer: final results of the MYME trial**


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**Background:** The potential antitumor effect of metformin (M) in breast cancer is being explored by several clinical studies, in early disease. In this phase II randomised study, we compare the efficacy of M plus first line chemotherapy (CT) versus CT in metastatic breast cancer (MBC).

**Methods:** 126 non-diabetic women (ITT 122) with stage IV, HER2 negative BC, untreated with CT, were randomized to Arm A: AC (non-pegylated liposomal doxorubicin 60 mg/m² + cyclofosfamide 600mg/m², x 8 Q21 + metformin 2,000 mg pos daily until progression) vs Arm B: AC. The primary endpoint was progression free survival (PFS). 98 PFS events were required for 80% power. Secondary endpoints were overall survival (OS), safety and outcome by insulin resistance status (HOMA Index ≥ 2.5).

**Results:** 122 patients are evaluable for primary endpoint. HOMA Index was > 2.5 in 57 overall survival (OS), safety and outcome by insulin resistance status (HOMA Index ≥ 2.5).

**Conclusions:** The present study does not provide evidence in support of an antitumor activity of M in combination with first line CT in MBC. Noteworthy, a significantly shorter PFS was observed in insulin-resistant patients (HOMA ≥ 2.5), without significant interaction with M. Further development of M in this setting is not warranted, while the adverse prognostic impact of insulin resistance needs to be addressed further.


**Legal entity responsible for the study:** IRST Meldola (FC), Italy

**Funding:** TEVA, Italian Association for Cancer Research (AIRC)

**Disclosure:** All authors have declared no conflicts of interest.

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### 219PD

**A phase II study of the cell cycle checkpoint kinases 1 and 2 (CHK1/2) inhibitor (LY2606368; prexasertib) in sporadic triple negative breast cancer (TNBC)**

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**Background:** CHK1/2 are major cell cycle regulators in tumors with p53 dysfunction, such as TNBC. Second-generation CHK1/2 inhibitor, prexasertib monosemolyte monophosphate, showed preliminary single agent activity in advanced cancer pts. We hypothesize that prexasertib may yield clinical benefit in sporadic TNBC pts.

**Methods:** Eligible pts have recurrent TNBC with no detectable germline BRCA mutation or no family history of hereditary breast and ovarian cancer syndrome, good end organ function and safety biopsiable disease. Prexasertib was administered at 105 mg/m² IV once every 14 days on a 28-day cycle. Response was assessed every 2 cycles by RECISTv1.1 and safety by CTCAEv4 per cycle. Primary endpoint is overall response rate (ORR). Optimal two-stage design was used, if ≥1 response is seen in the first 9 pts, then accrual continues to 24 pts per cohort.

**Results:** 9 wild type BRCA TNBC pts have been treated in the first stage (median age 55.3 yrs [29-72 yrs]) and median ECOG PS 1 [0-1]. The median number of prior therapies was 4 (2-10). 1 PR (3 mo) was observed (ORR 11%). 4 of 9 evaluable pts attained SD > 3 mo (median 4.5 mo [3-5]). Grade 3/4 AEs included neutropenia (89%), anemia (33%) and thrombocytopenia (22%). The median duration of grade 3/4 neutropenia was 5.5 (3-19) days. Grade 3/4 neutropenia resolved to less than grade 3/4 within 7 days in 5/9 pts. 1 pt required dose reduction to DL-1 (80 mg/m²) due to grade 4 neutropenia. 6 pts required G-CSF support to avoid treatment delays. 3 pts received pRBC transfusion due to grade 2/3 anemia. 1 pt with grade 3 thrombocytopenia required platelet transfusion to avoid procedure-related bleeding.

**Conclusions:** Prexasertib monotherapy showed modest single agent activity in sporadic TNBC pts and continues to enroll in second stage. Tri-lineage marrow toxicity was observed. Prophylactic GCSF should be considered.

**Clinical trial identification:** NCT02203513

**Legal entity responsible for the study:** National Cancer Institute, NIH Rockville, MD USA

**Funding:** This work was funded by the Intramural Program of the Center for Cancer Research, NCI, National Institutes of Health, USA

**Disclosure:** All authors have declared no conflicts of interest.

### 218PD

**Circling tumor cells as an early predictive marker of disease progression in metastatic breast cancer patients**

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**Background:** Circling tumor cells (CTCs) are a prognostic marker in metastatic breast cancer, but their predictive value to monitor treatment efficacy still needs further investigation. The aim of this study was to test whether persistent elevation of circulating tumor cells (CTCs) at both baseline and before 2nd cycle of a new treatment can serve as an early predictive marker of disease progression in patients with metastatic breast cancer using the predefined 5 CTC/75 ml threshold.
Methods: Eighty-five patients with stage IV breast cancer who met the eligibility criteria were enrolled in the study. Before starting a new treatment, all patients underwent full imaging studies and blood sampling for CTC enumeration. Patients with < 5 CTC<7.5 ml blood detected at baseline had no further CTC count. Patients with ≤ 5 CTC<7.5 ml blood had another blood sampling for estimation of CTC before the 2nd cycle (C2). Radiological assessment of disease status was done every 9 to 12 weeks. Disease response was assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST).

Results: At baseline, 44 (51.8%) of the 85 eligible patients did not have increased CTC levels. Of the other 41 patients with ≥ 5 CTC<7.5 ml blood, only 38 patients had CTCs evaluation at first follow-up before 2nd cycle (C2) that showed 23 (66.7%) patients had < 5 CTC<7.5 ml blood and 15 (39.5%) patients had ≥ 5 CTC<7.5 ml blood. Seventy-five patients (78/82, 91.5%) underwent radiological restaging. According to RECIST, 36 (48%) patients were scored as having a partial response, 19 (25.3%) as having stable disease, and 20 (26.7%) as having progressive disease. Radiologic response was concordant with follow-up CTC levels in 76.5% of cases. Survival of our patients depended significantly on both the results of CTC evaluation and radiological response. The median follow-up was 18.0 [1-60] months.

Conclusions: This study supports the significance of elevated CTCs before C2 in MBC patients starting a new line of chemotherapy as an early predictive marker of disease progression, thus, monitoring treatment benefit. It confirmed the independent prognostic value of CTCs.

Legal entity responsible for the study: The Ethics Committee of the Faculty of Medicine, Assiut University

Funding: Assiut University Hospitals

Disclosure: All authors have declared no conflicts of interest.

25SP Intratumoral heterogeneity of HER2 expression is relevant to breast cancer malignancy


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Background: Tumor diversity may cause therapeutic resistance and HER2 heterogeneity have been reported to associate with poor prognosis in esophagogastric adenocarcinomas. We focused on the correlation between HER2 heterogeneity and prognosis in breast cancer.

Methods: To determine the characteristics of heterogeneous overexpression of HER2 in breast cancer, we established two types of HER2-expressing cells, HER2-60 contains 63.2% of HER2-positive cells, and HER2-90 contains 92.4%, by introducing the HER2 gene into a human triple-negative breast cancer cell line, MDA-MB 231. We also investigated correlation between HER2 heterogeneity and tumor malignancy in human breast cancer specimens.

Results: When we inoculate the HER2-60 into the mammary fat pads of nude mice, heterogeneous HER2-expressing tumors developed, while HER2-90 consists mostly of HER2-expressing cells, and developed monotonous HER2-expressing tumors. We found that HER2-60 mice showed shorter survivals than HER2-90 mice, the median survival days after intracardiac injections were 24 (n = 22) and 30 (n = 13), respectively. Next we investigated the correlation between HER2 expression and prognosis in human breast cancer. There were 73 HER2-positive breast cancer patients who received neoadjuvant chemotherapy with trastuzumab and underwent surgery between January 2004 and December 2010 in our hospital. Fifty-five patients showed HER2+ by immunohistochemistry and 18 patients showed HER2+ and FISH-negative. HER2+ patients were divided into 2 groups by the staining pattern, overall and partially stained cases. We defined as HER2 monotonous-type (HER2 mono) and HER2 heterogeneous-type (HER2 hetero), respectively. At the median follow-up of 69.1 months, recurrent diseases were found in 25% (14/55) in HER2+ cases, and 30% (3/10) in HER2 hetero cases, while no recurrence was found in HER2 mono cases. Conclusions: Intratumoral HER2 heterogeneity is associated with aggressive breast cancers. Additional therapy should be considered for HER2 hetero breast cancers because HER2-positive breast cancers are all treated with chemotherapy with trastuzumab.

Legal entity responsible for the study: N/A

Funding: Grants-in-Aid for Scientific Research

Disclosure: All authors have declared no conflicts of interest.

25FP Phase II trial evaluating the combination of eribulin (E)+ bevacizumab (BEV) as first line chemotherapy in patients with metastatic Her2-negative breast cancer (MBC): a GINECO group study


Background: Phase III combination of chemotherapy with BEV versus chemotherapy alone in first line MBC showed a benefit in favour of the combination in terms of PFS. Moreover, paclitaxel + BEV is a standard of care in Europe, and the main toxicity is sensory neuropathy (23.5 % of grade >). The efficacy of E is well established in MBC pre-treated with taxanes and anthracyclines with a favourable safety profile. Therefore, our group initiated a study to assess the efficacy and safety of E + BEV combination in first-line MBC.
Efficacy and safety of nab-paclitaxel in patients with metastatic breast cancer: final results of the non-interventional study NABUCCO


Medical Department, IOMEDICO AG, Freiburg, Germany, Harrisst and Interstitial Onkologie, Krebszentrum Ratzeburg, Ratzeburg, Germany, Inner Medizin, Hämatologie and Interstitial Onkologie, Onkologische Gemeinschaftspraxis, Kassel, Germany, Hämatologie und Onkologie, Onkologische Schwerpunktpraxis Dr. Hansen & Reeb, Kaiserslautern, Germany, Innere Medizin, Hämatologie und Interdisziplinäre Onkologie, Hämato-Onkologische Schwerpunktpraxis, Munich, Germany, Clinical Operations, IOMEDICO AG, Freiburg, Germany, Internal Medicine / Hematology, Praxis für Interdisziplinäre Onkologie, Freiburg, Germany

Background: One of the most effective chemotherapies for metastatic breast cancer (MBC) is nab-paclitaxel (nab-P) which is approved for the treatment of MBC after failure of 1st-line therapy and when anthracyclines are not indicated. Randomized clinical trials have shown high efficacy and acceptable toxicity. Real world data of nab-P in MBC, however, are still limited.

Methods: The prospective multicenter non-interventional study NABUCCO was designed to collect data on the routine treatment of 700 patients (pts) with MBC in approximately 100 sites across Germany. Primary objective was the time to tumor progression (TTP), secondary objectives were overall response rate (ORR), overall survival (OS), the dosage scheme of nab-P, time on treatment, safety parameters and quality of life. Descriptive statistics were used to analyze the data. TTP and OS were calculated using the Kaplan-Meier method.

Results: Between 4/2012 and 4/2015 705 pts with MBC at 128 sites had been enrolled. 697 pts were evaluable with a median follow-up of 17.7 months. Baseline characteristics: Median age 62.3 years (range 29.2-89.3), age ≥70 years 236 (34.3%) of pts developed adverse events grade 3/4 which included leukopenia (7.9%) and infections (2.4%). Peripheral sensory neuropathy grade 1/2 was reported for 35.5% of pts and grade 3 for 4.3% of pts, respectively. Further subgroup analyses will be presented.

Conclusions: The results of the NABUCCO study confirm the clinical trial outcomes and the beneficial risk profile of nab-P in pts with MBC in a real-life setting.

Clinical trial identification: Projekt-Nr. IOM-02240

Legal entity responsible for the study: F Hoffmann-La Roche

Funding: F Hoffmann-La Roche

Disclosure: V. Mueller: VM has received speaker honoraria from Amgen, AstraZeneca, Celgene, Eisai, GlaxoSmithKline, Pfizer, Pierre Fabre, NavoCare, Roche, Teva and Janssen-Cilag, and consultancy honoraria from Roche, Pierre Fabre, Amgen and Eisai. S. de Duca: SdD is an employee of Roche and holds shares in Roche. L. Mitchell: F Hoffmann-La Roche

Background: Real-world data exploring effectiveness of treatments following demonstrated efficacy in phase III trials are becoming increasingly important, especially for regulatory bodies and payers. Pooling outcome and adverse-event (AE) data from non-interventional studies enables more accurate estimation of real-world effectiveness and safety in clinically important subgroups.

Methods: Individual pt data from pts receiving first-line BEV + PAC with no additional chemotherapy agent for HER2-negative MBC in three non-interventional studies (ML21165 [Germany], AVANTI [Germany] and AVAREG [Hungary]) were extracted and pooled. Progression-free survival (PFS) and overall survival (OS) were estimated in the BEV + PAC population and subgroups of clinical interest by Kaplan-Meier methodology: Safety was analysed descriptively.

Results: The analysis population included 2155 pts. The median duration of follow-up was 13.1 (range 7.9-17.2) months. The median BEV treatment duration was 5.4 (range <0.1-45) months; 205 pts (10%) received BEV for ≥1 year. Treatment was stopped because of disease progression/death in 42% of pts and AEs in 7%. Median PFS and OS were 8.7 and 21.0 months, respectively, and varied according to established risk factors (table). There were no relevant differences in the incidence of grade ≥3 hypertension in pts with ECOG PS 2 (1%) vs <1 (1.3%) and age ≥70 (3.1%) vs <70 (2.4%) yrs. The exposure-adjusted incidence of hypertension was 0.847 vs 0.653 events/pt-year in pts ≥70 vs <70, respectively.

Table: 237P

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<td></td>
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<td>Median, months (95% CI)</td>
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<tr>
<td>All</td>
<td>1366/2124 (64)</td>
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<td>7.0 (6.2-7.8)</td>
</tr>
<tr>
<td>Prior anthracyclines and/or taxanes</td>
<td>750/899 (86)</td>
<td>8.1 (7.7-8.5)</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>861/1233 (70)</td>
<td>8.3 (7.9-8.8)</td>
</tr>
<tr>
<td>Low risk (1 risk factor)</td>
<td>586/1289 (75)</td>
<td>10.0 (9.3-10.7)</td>
</tr>
<tr>
<td>Moderate risk (2 risk factors)</td>
<td>668/862 (78)</td>
<td>8.6 (8.1-9.1)</td>
</tr>
<tr>
<td>High risk (3 or more risk factors)</td>
<td>255/395 (75)</td>
<td>6.7 (5.9-7.2)</td>
</tr>
</tbody>
</table>

Conclusion: Results from >2000 pts treated in the real-world setting indicate effectiveness of first-line BEV + PAC in HER2-negative MBC. The main limitation of this analysis is the inconsistent data collection and recording between studies. Nevertheless, this approach provides insight into effectiveness of BEV + PAC in the real-world setting.

Clinical trial identification: N/A

Legal entity responsible for the study: F Hoffmann-La Roche

Funding: F Hoffmann-La Roche

Disclosure: V. Mueller: VM has received speaker honoraria from Amgen, AstraZeneca, Celgene, Eisai, GlaxoSmithKline, Pfizer, Pierre Fabre, NavoCare, Roche, Teva and Janssen-Cilag, and consultancy honoraria from Roche, Pierre Fabre, Amgen and Eisai. S. de Duca: SdD is an employee of Roche and holds shares in Roche. L. Mitchell: F Hoffmann-La Roche
Eribulin is effective and safe as first-line therapy for aggressive taxane-resistant HER2- [MBC] patients (pts)

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Background: Eribulin improved overall survival (OS) in 2.3 line treatment of MBC pts. In a large retrospective study, short disease-free interval (DFI) and prior taxane therapy have been associated with worse OS in pts receiving first-line chemotherapy for HER2-[MBC]. The aim of the MERBEL study was to evaluate the efficacy and safety of eribulin as first-line therapy for HER2-[MBC] pts with these poor prognostic factors.

Methods: Phase II, multicenter, single arm, trial. Eribulin (1.23 mg/m2) was administered on days 1 and 8 of 21 day cycles until progression or unacceptable toxicity. Principal selection criteria: (1) HER2-[MBC] pts without prior chemotherapy for MBC; (2) prior taxane therapy (2 cycles) for early BC; (3) less than 36 months (mo) between the last taxane cycle and relapse; (4) RECIST 1.1 evaluable disease; (5) no symptomatic or symptomatic disease involving evaluable organ sites were observed. Eribulin was given every 3 weeks (WW) from the time of progression (TTP). Secondary endpoints included OS, progression-free survival (PFS), objective response rate (ORR), clinical benefit rate (CBR) and toxicity. We included 53 women from 61 pts recruited between SEP/2013 to MAR/2015 across 12 sites and 2 countries.

Results: Median age 51 years [range 23-83]; 50.9% were ECOG 0; 43.5% were triple-negative; 84.9% received prior anthracyclines. Median DFI was 15.7 mo [0.1-146.5]; and 52.8% had visceral metastases (11.3% with ≥3 involved organ sites). Median follow-up was 12.7 mo [0.2 – 30.5]. Median TTP was 4.1 mo [95%CI 2.2-6.5]; median OS was not yet reached. In the 1-year TTP, PFS and OS rates were 16.2%, 24.3%, and 65.9%, respectively. The ORR was 20.8% and CBR, 26.4%. Eribulin all grades and 3/4 adverse events (AEs) were reported in 96.2% and 71.7% of the pts, respectively. The most common grade 3/4 AEs were neutropenia (28.3%), leukopenia (17%), peripheral neuropathy (5.7%) and asthenia (5.7%). One patient experienced febrile neutropenia. Percentages of pts with AEs leading to treatment discontinuation, reduction, or delay were 15.1%, 9.4%, and 26.4%, respectively.

Conclusions: Eribulin is effective and safe as first-line therapy for aggressive taxane-resistant HER2-[MBC] pts with these poor prognostic factors.
Results: From October 2013-October 2015, 77 pts ≥70yrs retrospectively identified from the RMH Pharmacy Data Base received capcitabine monotherapy for MBC. Capicitabine was 1st line therapy in 65 pts (84%), with 43pts & 34 receiving 2000mg/m² & <2000mg/m² respectively (25pts-1500mg/m², 10pts-1000mg/m²). Pts starting at a lower dose were older (79 yrs vs 73 yrs, p < 0.001), with more moderate to severe renal impairment (16% vs 4%, p = 0.016). ECOG PS ≥2 (11% vs 26%, p = 0.156) & more advanced metastatic disease (17% vs 35%, p = 0.09). With respect to toxicity: 8 pts (19%) in the 2000mg/m² group had grade 3-4 toxicities vs 1 pt (3%) in the <2000mg/m² group. 9% vs 91% in the <2000mg/m² and 2000mg/m² groups respectively required D/R. 42% in 2000mg/m² vs 32% in the <2000mg/m² group switched to WOWO due to early toxicity. No treatment related deaths were observed. CBR for 2000mg/m² & <2000mg/m² groups was 67% vs 43% respectively (p = 0.09). After a median follow-up of 28.1 months, the combined TTP was 8.2months & OS of 18.6 months. TTP was 11.7 months and 6.2 months in the 2000mg/m² & <2000mg/m² groups respectively (p = 0.111).

Conclusions: In patients aged 70 years or older, capcitabine monotherapy at a starting dose of 2000mg/m² or lower is associated with a median TTP of 8.2 months and a CBR of 43-67%. Toxicity can be managed by dose reductions and switching to a WOWO dose of 2000mg/m² or lower is associated with a median TTP of 8.2 months and a CBR of 43-67%. Toxicity can be managed by dose reductions and switching to a WOWO dose of 2000mg/m² or lower is associated with a median TTP of 8.2 months and a CBR of 43-67%. Toxicity can be managed by dose reductions and switching to a WOWO dose of 2000mg/m² or lower is associated with a median TTP of 8.2 months and a CBR of 43-67%. Toxicity can be managed by dose reductions and switching to a WOWO dose of 2000mg/m² or lower is associated with a median TTP of 8.2 months and a CBR of 43-67%. Toxicity can be managed by dose reductions and switching to a WOWO dose of 2000mg/m² or lower is associated with a median TTP of 8.2 months and a CBR of 43-67%.
unknown. In 14 patients MBC was present at time of primary diagnosis. Prior treatment consisted of adjuvant endocrine treatment (17/35 HR+ patients), adjuvant CT (n = 7) and palliative hormonal treatment (29/35 HR+ patients). Most patients (n = 42) received single agent CT, consisting of capecitabine (n = 15), 13 adriamycin (n = 10), paclitaxel (n = 6), vinorelbine (n = 4) or 5-fluorouracil (n = 3). Combination CT was given to 11 patients. A total of 28 patients (52%) had clinical benefit (defined as ≥6 months progression-free survival (PFS)). Median PFS and median overall survival (OS), analyzed according to Kaplan-Meier, from start of palliative CT were 6.8 months (95% Confidence Interval (CI) 4.8 – 8.8) and 14.4 months (95% CI 10.3 – 18.6), respectively. PFS and OS did not differ significantly between single agent or combination CT (p < 0.05). CT was stopped because of PD or toxicity in 32 and 13 patients (62% and 25%), respectively.

Results: Even in elderly MBC patients, palliative chemotherapy may have clinical benefit in selected patients aged 75+. Single agent CT seems feasible and effective, but 25% of patients discontinued CT due to toxicity.

Clinical trial identification: N.A.

Legal entity responsible for the study: Netherlands Cancer Institute - Antoni Van Leeuwenhoek

Funding: Netherlands Cancer Institute - Antoni Van Leeuwenhoek

Disclosure: All authors have declared no conflicts of interest.

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**Eribulin mesylate may improve the sensitivity of endocrine therapy in metastatic breast cancer**

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**Background:** Eribulin mesylate (ER) is a microtubule dynamics inhibitor that has been demonstrated to prolong overall survival in metastatic breast cancer. Recently, ER has shown to reduce the abnormality of the tumor microenvironment. Endocrine therapy has been reported to be ineffective under hypoxic conditions; however, improved oxygenation of the peritumoral area due to ER may increase the sensitivity of endocrine therapy. Generally, the efficacy of endocrine therapy at late-line treatment is inferior to that of endocrine therapy at early-line. Hence, we hypothesized that endocrine therapies following ER administration might be more effective.

**Methods:** Since the approval of ER in Japan, 178 patients with metastatic breast cancer received ER from August 2011 to October 2014 at the Cancer Institute Hospital of JFCR. Of those, we assessed the time to treatment failure (TTF) of endocrine therapies provided to 25 postmenopausal patients in whom at least two endocrine therapies had been performed before ER and at least one endocrine therapy after ER. We retrospectively analyzed the effectiveness of the endocrine therapies on the basis of intraindividual changes.

**Results:** In these 25 cases, TTF of endocrine therapy before ER administration (N-1) was longer in 6 cases (24%) compared with that of N-2, which is another endocrine therapy before N-1. In contrast, TTF of endocrine therapy after ER administration (N) was found to be longer than that of N-1 in 16 cases (64%). Thus, the ratio that the TTF of late endocrine therapy was longer than that of early endocrine therapy was significantly higher (p = 0.018) when the ER administration was inserted between endocrine therapies.

**Conclusions:** In the present study, ER administration between two endocrine therapies prolonged the TTF in majority of the cases, and ER might improve the sensitivity of endocrine therapy.

Legal entity responsible for the study: Kokoro Kobayashi

Funding: Cancer institute hospital of JFCR

Disclosure: Y. Hiro - Research grants from Novartis, Chugai, and Asahi Kasei; Former employee of Sanofi Honorarium from Eli Lilly; S. Takahashi: Honorarium from Eisai. S. Ohno - Honoraria from Chugai and AstraZeneca. All other authors have declared no conflicts of interest.

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**Maintenance metronomic chemotherapy combined with conventional treatment for metastatic breast cancer patients**

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**Background:** The treatment duration for metastatic breast cancer patients remains a controversial issue. Despite no overall survival benefit for conventional chemotherapy with increased toxicity. This study was carried out to evaluate the benefit of adding metronomic chemotherapy to conventional treatment regarding progression free survival, response rate and toxicity.

**Methods:** Patients received first line treatment for their metastatic disease either chemotherapy followed by maintenance metronomic chemotherapy with or without hormonal therapy or primarily treated with hormonal therapy concomitant with metronomic chemotherapy. Metronomic chemotherapy consists of cyclophosphamide 50 mg tablet daily and metothexate 2.5mg twice daily on days 2 and 5 weekly, continued until disease progression or development of unacceptable toxicity. Her2 +ve patients didn’t receive trastuzumab.

**Results:** After median follow up of 24 months (range: 9 months – 30 months), 40 patients were assessed, the progression free survival was 42.5% and the median time to disease progression was 10.6 months. The overall clinical benefit (CR + PR + SD) was 42.5% with no G3/4 toxicities encountered for metronomic therapy. Only G1/2 leucopenia (40%), G1/2 gastritis (62.5%), one patient developed grade 3 increased transaminases and resume treatment with 50% dose reduction. The median time to disease progression was 13.5 months for ER +ve, Her2 +ve compared to 8.5 months for ER +ve, Her2 + ve, 8 months for ER +ve,Her2 +ve and 8 months for triple negative. The difference was statistically significant (P value = 0.018). Univariate and multivariate analysis found that ER –ve, Her2 +ve and the presence of visceral metastasis are the most significant negative prognostic factors for time to disease progression whereas patients with bone only metastasis and ER + ve, HER2 neu –ve have the best outcome.

**Conclusions:** Maintenance metronomic cyclophosphamide and methotrexate demonstrated efficacy and provided durable disease stabilization especially for ER positive patients. The low costs and minimal toxicity support its use as an additional therapeutic tool.

Clinical trial identification: 1/29/26/1/2014

Legal entity responsible for the study: Ethics committee, Alexandria University

Funding: Ayady AlMostakbal Oncology Center (AAOC)

Disclosure: All authors have declared no conflicts of interest.
Background: Data on the combination of eribulin and trastuzumab (E/T) are limited, although recent analyses demonstrated safety and efficacy for its use. The aim of this Italian multicenter experience was to examine the tolerability and the clinical activity of eribulin plus trastuzumab in the treatment of HER2 positive ABC.

Methods: Patients (pts) treated with eribulin mesylate (1.23 mg/m² on days 1 and 8 of a 21-day cycle) plus standard dosing of trastuzumab (16 pts received 3-week schedule: 8 mg/kg every 3 weeks; 8 pts received weekly schedule: 4 mg/kg load, 2 mg/kg q-w) in 6 Italian oncology units were included. Data on response rate (RR), overall survival (OS) and safety were reported.

Results: Between October 2012 and November 2015 twenty four pts with HER2-positive ABC were included. Median age was 57 years (32-to-74). All patients were heavily pretreated: the median number of prior chemotherapy (CT) regimens for MBC was 3 (range 2-9). ECOT PT pre-E/T treatment was 0.1 in 75%. The median number of cycles with E/T was 11.5 (range 2-26). Complete response (CR) was achieved in 1 pts (4.2%), 9 pts (37.5%) achieved partial response (PR), 9 pts (37.5%) achieved stable disease (SD), and 5 pts (20.8%) had progressive disease (PD). Median OS was 7.7 months (range 2.8-30.5). Comorbidities at study entry were cardiovascular (including hypertension), 54.2%, diabetes, 8.3%, other diseases, 16.7%. Neutropenia was the most common grade 3/4 adverse event (23%); one case (4.2%) of febrile neutropenia was observed. Main grade 3/4 non hematological toxicities were fatigue (4.2%), peripheral neuropathy (4.2%) and nausea (4.2%). Alopoea was observed in more than half of pts (66.7%). Dose reduction was applied in 6 pts (25%); three pts (12.5%) interrupted the treatment prematurely.

Conclusions: Tolerability and efficacy of E/T combination schedule are encouraging. The results of this study indicated that this combination might be considered for future prospective study.

Legal entity responsible for the study: Savero Ciniert

Funding: Medical Oncology Group Ospedale Perrino Brindisi

Disclosure: All authors have declared no conflicts of interest.
Conclusion: Patients with a low number of BM from MBC who had aggressive treatment with surgery or SRS have a favorable outcome. WBRT use should be delayed as much as possible, to avoid neurocognitive sequelae.

Legal entity responsible for the study: Centre Leon Berard
Funding: Centre Leon Berard
Disclosure: All authors have declared no conflicts of interest.

Background: Overall survival (OS) is considered the gold standard for clinical benefit in oncology trials, but mature data are often unavailable. A relationship between progression-free survival (PFS) and OS in advanced cancer, including breast cancer (BC), is known: FDA (2007) suggests PFS may be a surrogate for OS; a NICE DSU report (Davis et al 2012) presents evidence of a relationship between PFS and OS in BC. This analysis further examined the relationship between PFS and OS with a view of using PFS as a predictor of OS using data from the Phase II FIRST study (n = 205; NCT00274469) of fulvestrant 500 mg vs. anastrozole as first-line treatment in hormone-receptor positive advanced BC.

Methods: In the interests of homogeneity, the relationship between PFS and OS was evaluated in endocrine-naïve patients in the FIRST study (n = 73 [72%] fulvestrant; n = 80 [78%] anastrozole) by substituting the linear expression into each other and using Weibull parametric fits and linear regression. PFS and OS data from a study of anastrozole in a similar population (Nabholtz et al 2000, 2003) were applied to validate the Weibull and linear regression model.

Results: Using log cumulative hazard plots, a linear trend was shown for PFS and OS. From the Weibull model, relationships between OS and PFS were derived for: given S, number surviving, fulvestrant In time_OS(S) = 0.82 + 0.80 ln time_PFS(S); and anastrozole ln time_OS(S) = 0.897 + 0.79 ln time_PFS(S). Based on linear regression of part of the PFS and OS curve (driven by apparent deviation from a linear relationship), the following relationships were derived: fulvestrant In time_OS(S) = 0.77 + 0.63 ln time_PFS(S); and anastrozole ln time_OS(S) = 0.95 + 0.67 ln time_PFS(S). In all equations, time = days/1000. Applying both models to other clinical data for anastrozole showed a good fit and thus extends this relationship beyond the FIRST study.

Conclusion: This analysis shows a novel, validated approach by which the relationship between PFS and OS in patients receiving first-line treatment with fulvestrant or anastrozole can be modelled. These results add to the acceptance of PFS as a predictor of OS in this setting.

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Legal entity responsible for the study: AstraZeneca
Disclosure: M. Ouwens, L.M. Grinsted, C. Telford: Employment, stock or other ownership - AstraZeneca

Clinical decision making in patients with metastatic breast cancer in the United Kingdom (UK) and Italy

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Background: Several treatment options are available for metastatic breast cancer (MBC), but guidelines may not specify, for example, the nature, number and sequence to be used. The aim of this study was to compare treatment strategies between two oncology Centers in the UK and Italy.

Methods: We retrospectively collected disease characteristics, demographic and treatment data of 228 consecutive patients (pts) diagnosed with MBC at the University Hospitals of Leeds (UK) and Udine (Italy) between January 2012 and December 2013 who received at least one line of therapy. The cohorts were compared using Chi square test or Fisher exact test as appropriate. Overall Survival (OS) was analysed by log rank test.

Results: We identified 120 UK and 108 Italian pts; median follow-up from the diagnosis of MBC was 41 and 38 months, respectively. The UK and Italian patients were similar with respect to clinical and pathological characteristics. Median age was 64 years; hormone receptor (HR) +ve rates were 88% vs. 80% for the UK and Italian pts, respectively while 26% and 24% of pts respectively were classified as HER2 +ve. When diagnosed with MBC, visceral metastases were present in 54% vs. 47% of the UK and Italian pts, respectively. Fifty-one percent of UK pts and 43% of Italian pts underwent biopsy before first line treatment for MBC. The number of systemic treatment lines was the same for the two Centers (median 2; range 1-7). Analyzing first line treatment, a similar proportion of UK and Italian pts with HR +ve/HER2 -ve disease received endocrine therapy (55% vs. 49%) and chemotherapy (45% vs. 51%); the presence of visceral metastases increased the likelihood of chemotherapy being preferred as first line therapy in the UK but not Italy (64% vs 52%, respectively). As of December 2015, 63% and 56% of pts from Leeds and Udine, respectively had died. The median OS was 28 vs 27 months for the UK and Italian pts, respectively. No significant differences were observed in the time between the start of the final line of systemic therapy and death (7 vs. 8 month in UK and Italian pts, respectively).

Conclusion: So far, we have not identified significant differences in the management of MBC pts between the two Centers on OS outcomes between English and Italian pts. More detailed analyses are ongoing.

Funding: University of Udine
Disclosure: All authors have declared no conflicts of interest.

Long lasting survival (LLS) after removal of primary tumor (PT) in metastatic breast cancer (MBC). Impact of age on outcome

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Background: Retrospective evidence suggest an impact of the local control on survival in patients with MBC. A potential cause is the presence of LLS after PT removal. The aim was to assess the proportion of LLS after PT removal versus no surgery and the impact of age.

Methods: A retrospective study was performed between February 1982 and September 2005 in our institution. In order to minimize selection bias patients > 80y, with median follow-up >90 days and Charlson score >2 were excluded. An univariate and multivariate analysis of survival with other prognostic variables was performed. Overall survival (OS) was calculated with Kaplan-Meier (KM). Probability of LLS was considered for patients with survival >120 months. Analyses were performed for the whole series, <65 and >65 years old cohorts.

Results: 192 pts with MBC at diagnosis were recruited, of whom 112 underwent excision of the PT (Surgery group) and 80 pts did not received local therapy (Non-surgery group). Median age was 56 (48-65) for Surgery and 59 (51-70) for Non-surgery group. Operated patients were more likely to have only 1 site of metastasis. In the univariate analysis removal of PT, ER, PR, PS and number of metastatic sites were significantly related with OS. However only removal of PT and ER remained as independent prognostic factors in the multivariate analysis. With a median follow-up of 67.7 months, OS was significantly superior in Surgery group (40.7 vs 22 months, p < 0.001). Proportion of LLS was 16.7% vs 4.4% in surgery vs non-surgery group. KM for OS in the subgroup of < 65 showed similar results with median of 40.7 vs 22 months (p < 0.001) and LLS of 19.9% vs 2.1%. In this group removal of PT, ER and bone-disease only were significant in multivariate analysis. Of note in >65 years surgery had no benefit in OS (log rank p = 0.340) and LLS of 14.0% vs 8.1% in surgery vs non-surgery group. In this group Charlson score was a significant prognostic factor for survival in this cohort.

Conclusions: Surgical excision of PT in younger patients with ER+ and small number of metastatic sites seems to have an impact in achieving an important proportion of LLS. No benefit in >65 years was seen.

Legal entity responsible for the study: Instituto de Investigacion Clinico Valencia (INCLIVA) Hospital Clinico Universitario Valencia
Funding: Instituto de Investigacion Clinico Valencia (INCLIVA) Hospital Clinico Universitario Valencia
Disclosure: All authors have declared no conflicts of interest.

The difference in prognostic outcomes between de novo stage IV and recurrent metastatic patients with hormone receptor-positive, HER2-negative breast cancer: a single-center study

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Background: The difference in prognostic outcomes between de novo stage IV and recurrent metastatic breast cancer is still unclear, and these patients have often been treated with the same treatment strategies. The objective of this retrospective single-center study was to compare prognostic outcomes between these patients, in
particular patients with hormone receptor-positive (HR+), HER2-negative (HER2-) metastatic breast cancer. This analysis may help us to interpret results from current clinical research and propose future studies. 

Methods: This is a chart review study of de novo stage IV and recurrent metastatic patients with HR+ or HER2- breast cancer, who were treated between January 2008 and December 2015 in Sakai City Medical Center, Japan. We used the Kaplan-Meier method to estimate overall survival of the two groups. The Cox proportional hazards model was used to examine the prognostic evaluation between the groups by using two prognostic indicators: disease-free interval (DFI) and interval from the end of adjuvant treatment to the first recurrence (AFI).

Results: We studied 145 patients, including 52 de novo stage IV and 93 recurrent metastatic patients with HR+ or HER2- breast cancer. There was no significant difference in prognosis between the groups. However recurrent patients with DFI < 2 years were found to have significantly poorer prognosis compared with recurrent patients with DFI ≥ 2 years (hazard ratios (HR): 2.20, 95%CI:1.46-3.87, p = 0.016), and de novo stage IV patients (HR:2.843, 95%CI:1.473-5.489, p = 0.002). Similarly, recurrent patients with AFI < 1 year had significant poorer prognosis compared with de novo stage IV patients (HR:1.330, 95%CI:1.034-1.711, p = 0.026).

Conclusions: De novo stage IV breast cancer patients had better prognosis due to therapy-naive or less resistant metastastic disease compared with recurrent patients with DFI < 2 years or AFI < 1 year, who were likely to have an insufficient or non-carry-over effect of adjuvant treatment. If future efforts are conducted with a larger spectrum of patients and treatment analysis, results might be more conclusive.

Legal entity responsible for the study: Sakai City Hospital Organization

Funding: Sakai City Hospital Organization

Disclosure: All authors have declared no conflicts of interest.
Background: Brain metastases (BM) occur in 15-30% of patients with metastatic breast cancer (MBC). In spite of improvements in the treatment, the development of BM is still being a major limitation of life expectancy and quality of life for many patients (P).

Methods: Ambispective analysis of MBC patients who developed single or multiple BM and were treated in a single cancer comprehensive center. Identification of patients and updates of follow up were performed through Radiation Oncology department registries and Pathology Records. Breast Graded Prognostic Assessment (GPA) was calculated according to Sperduto GPA (2012).

Results: From 2007 to 2014, 133 patients were identified, 30(22.6%) were diagnosed at de novo IV stage. Median age at BM diagnosis 52.3 years (29.7-81); 53.9% were luminal (LT), 42 (31.6%) HER2 positive (Her2), 31 (23.3%) triple negative (TN) and 7 cases unknown. Median FPS was 28 and median time to BM after cancer diagnosis (TBM) was 41 (714 m in LT; 26 in Her2 and 2 in TN (p = 0.002). Her2 showed more incidence of BM as first relapsed (17.5%) than others subtypes (11.1% LT and 13.5% TN p = 0.002). 45 P (33.8%) had a solitary BM, 50 (36.7%) had ≥2 lesions and 25 (23.8%) more than 3, and 3 unknown. No correlation between number of lesions and histological subtypes was found. Breast-GPA (0-1): 12%, (1.5-2): 26.3%, (2.5-3): 24.6% and (3.5-4): 25.6% were treated with stereotactic radiosurgery (SRS), 21% surgery (S) and 76% WBRT. Median survival after BM (BMS) was 12 m (7-17). BMS according GPA was (0-1) 8m (1.5-2) 6m, (2.5-3) 19m and (3.5-4) 30m (p = 0.001). BMS according number of BM: 1 lesion 21m (8.9-33), 2-3 lesions 10 m (5.7-14) and >3 lesions 8 m (5-11) and according subtypes LT 11 m (4-18),TN 8m (4.5-115) and Her2 26m (7-45). Local treatment with SRS and S prolonged BMS (28 vs 8 m p= 0.001) as well as the administration of chemotherapy (29 vs 10 p = 0.032). Significant prognostic factors by multivariate Cox regression were GPA (HR 0.7 CI 0.55 0.91 p = 0.008) and number of lesions (HR 1.3 CI 1.03 1.79 p = 0.027).

Conclusions: Breast-GPA, number of lesions and type of treatment are the most important prognostic factors for MBC patients with BM. Multidisciplinary treatment should be decided according to these factors.

Legal entity responsible for the study: Jover ena Linares Aceituno

Funding: Catalan Institute of Oncology

Disclosure: All authors have declared no conflicts of interest.

Impact of the biological subtype on the risk of developing brain metastasis in Egyptian breast cancer patients

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Background: We aimed at investigating the impact of the biological subtype of breast cancer on the risk of developing brain metastasis and the outcome of Egyptian patients with brain metastasis.

Methods: We retrospectively reviewed the clinical records of 2193 consecutive women (1947 with localized disease and 246 with metastatic disease at presentation) diagnosed with breast cancer between January 1999 and December 2010. We explored the relationship between the clinicopathological factors (including the biological subtypes) and the incidence of brain metastasis, Brain metastasis free survival (BMFS), and the Brain metastasis specific survival (BMSS).

Results: Median follow up period for the whole cohort was 43.5 months (IQR 26-74 months). 160 patients (7.3%) developed brain metastasis. Among the individual clinicopathological parameters, larger tumors (p = 0.006), axillary LN positivity (p < 0.001), high grade (p = 0.006) and HER2 positivity (p < 0.001) were associated with higher incidence of brain metastasis. By Kaplan Meier model, and in those presenting with localized disease, the HER2-rich subtype was associated with the poorest BMFS (by BMFS: 77.6%) followed by Triple negative and Luminal B diseases (by BMFS: 80.9% and 81.3%) with the longest BMFS in the Luminal A subtype (by BMFS: 88.2% for trend p = 0.002). In the multivariate model, only 3 factors remained independent predictors for developing brain metastasis; tumors larger than 2 cm (HR = 3.60 95CI: 1.54-8.38; p = 0.003), axillary LN metastasis (HR = 4.03 95CI: 1.91-8.52; p < 0.001) and HER2-rich subtype (HR = 1.85; 95CI: 0.99-3.45; p = 0.051).

Regarding the outcome of the 160 patients with brain metastasis, BMSS was highest in the Luminal A patients (Median 31 m) followed by Luminal B (Median 8.3m) with poorest BMSS among HER2 rich and triple negative patients (median 7.9m and 7.6m respectively; p = 0.024).

Conclusions: Breast cancer biological subtype plays a pivotal role in predicting the pattern of failure of patients presenting with localized disease and the subsequent outcome after brain metastasis in addition to the classical prognostic factors.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Site of first recurrence of breast cancer after adjuvant therapy: Clinical aspects and outcome analysis

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Background: The objective of this retrospective study was to characterize the sites of first relapse in a cohort of Tunisian patients with metastatic breast cancer relapsing after adjuvant therapy and to report survival on each site.

Methods: Among 1400 early breast cancer patients treated from 2000 to 2010, 324 (23%) relapses were divided into 4 groups according to first site of appearance: A- locoregional alone (breast and lymph nodes), B-Bone alone, C-Brain alone and D- Other sites. Controlateral breast cancer was excluded. Clinico-pathological aspects and initial therapy were studied for each group. Survival results were reported.

Results: In group A, 12 patients had local recurrence (8 after breast-conserving surgery), 37 patients had nodal recurrence (23 axillary, 14 sub-clavicular and 11 had both). Nine patients had surgical resection, 19 had radiation therapy and all patients received chemotherapy. In group B, 35 patients had palliative radiation, 50 had chemotherapy, 15 patients were available for 67 patients. In group C, we observed 4 cases of meningal carcinomatosis, one case was operated, and all other cases had whole brain radiation. In group D, metastases were: liver (43), lung (32), pleural (27), peritoneal (12), gastric (5) and other (32). Seven patients had initial endocrine therapy, 3 patients had metastasectomy (2 liver, 1 lung) and the remaining had chemotherapy.

Table: 259P Patient characteristics according to site of recurrence

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>47</td>
<td>48</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Progesterone</td>
<td>34 (56%)</td>
<td>54 (69%)</td>
<td>45 (68%)</td>
<td>44 (59%)</td>
</tr>
<tr>
<td>Age +35</td>
<td>35 (55%)</td>
<td>54 (69%)</td>
<td>45 (68%)</td>
<td>44 (59%)</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>0.3</td>
<td>0.6</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>SBR II-III</td>
<td>27</td>
<td>35</td>
<td>45</td>
<td>56</td>
</tr>
<tr>
<td>PR+</td>
<td>44 (75%)</td>
<td>64 (79%)</td>
<td>54 (79%)</td>
<td>65 (91%)</td>
</tr>
<tr>
<td>Immunohistochemistry (available data)</td>
<td>HR + HER2</td>
<td>HR2</td>
<td>HR2</td>
<td>HR2</td>
</tr>
<tr>
<td>44 (75%)</td>
<td>64 (79%)</td>
<td>54 (79%)</td>
<td>65 (91%)</td>
<td></td>
</tr>
<tr>
<td>HR + HER2</td>
<td>44 (75%)</td>
<td>64 (79%)</td>
<td>54 (79%)</td>
<td>65 (91%)</td>
</tr>
<tr>
<td>HER2</td>
<td>44 (75%)</td>
<td>64 (79%)</td>
<td>54 (79%)</td>
<td>65 (91%)</td>
</tr>
<tr>
<td>Time to relapse (months)</td>
<td>60</td>
<td>44</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>44</td>
<td>44</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>2 years survival (%)</td>
<td>60</td>
<td>44</td>
<td>44</td>
<td>44</td>
</tr>
</tbody>
</table>

Overall survival at 2 years was 49% (median of 37 months) after median follow-up of 67 months. Site of initial recurrence favoring loco-regional and bone locations (p < 0.0001) and time to relapse (p = 0.0006) were important determinants for predicting survival from the time of initial recurrence.

Conclusions: In Tunisia, patterns of relapse according to first site of appearance are similar to results reported in the literature, being characterized by young age, large tumor size and aggressive histological features.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

An abstracts
Impact of palbociclib plus fulvestrant on patient reported general health status compared with fulvestrant alone in HR + , HER2- metastatic breast cancer


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Background: The present analyses compare patient reported general health status between palbociclib plus fulvestrant and fulvestrant alone in HR + , HER2- metastatic breast cancer.

Methods: Patients in PALOMA-3 study (NCT 01942135; Turner et al. NEJM 2016) were randomized to palbociclib plus fulvestrant (n= 347) or placebo plus fulvestrant (n= 174). Patient-reported outcomes were assessed at baseline, on day 1 of each cycle until cycle 4 and every alternate cycle from cycle 4 until end of treatment using EQ-5D, a standardised measure of health status that consists of a descriptive system comprising 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression rated at 3 levels (no problem, some problem, and a single index score for health status (range 0 [worst imaginable] to 1 [full health]) calculated using a standard algorithm. In a visual analog scale (VAS) measured self-rated health status from '0' (worst imaginable) to '100' (best imaginable). Repeated measures mixed-effects analyses were performed to compare overall index and VAS scores between treatments, contrasting for baseline.

Results: Completion rates at baseline were ≥85% in each group. The mean (SD) scores at baseline were comparable between palbociclib plus fulvestrant and fulvestrant alone for the VAS (72.9 [17.2] vs 70.3 [15.9]) and the EQ-5D index scores (0.73 [0.23] vs 0.71 [0.23]). General health status assessed by VAS was found to be maintained from baseline and no significant difference in overall EQ-5D VAS scores was observed between the treatment arms. The proportion of patients reporting the presence of a problem at baseline was lower for palbociclib plus fulvestrant and fulvestrant, respectively: mobility (28% vs 32%), self-care (9% vs 9%), usual activities (38% vs 45%), pain (67% vs 67%), and anxiety/depression (52% vs 61%). The overall mean EQ-5D index scores on treatment was significantly greater (p < 0.05) for palbociclib plus fulvestrant (0.74) compared with fulvestrant alone (0.69).

Conclusions: Addition of palbociclib to fulvestrant was associated with significantly higher on treatment EQ-5D index scores compared to fulvestrant alone.

Clinical trial identification: NCT01942135

Legal entity responsible for the study: Pfizer

Funding: Pfizer, Inc

Disclosure: S. Lobl: Research and funding and honoraria to institution from GlaxoSmithKline, Novartis, Roche Pharma AG; Pfizer,Celgene, Amgen, and most other pharmaceutical companies. A. Demichele: Participant on Advisory Board sponsored by Pfizer. N.M. Turner Consultant: Advisory role and receives honoraria from AstraZeneca; Pfizer, Roche Pharma AG. M. Cristofanilli: honoraria - Agenda; Cyvenio Biosystems; Dompé Farmaceutici Consulting/Advisory role-Cyvenio Biosystems; Dynomics/Scriptor’s bureau- Agendia; NanoString Technologies. S. Loi: Affiliated Institute receives research funding from PharmaSas. S. Verma: Advisory Board Member for Pfizer, Roche, AZ, Novartis, Amgen, Eisai/BMS, EL Lilly and Merck. H. Bhattacharyya: Pfizer employee and stockholder. Z. Ke, C. Giorgetti, C.H. Bartlett: Pfizer Employee and Stockholder. S. Iyer: Employee and shareholder/stock options owner of Pfizer, Inc. M. Colleoni: Honoraria - Novartis Advisory Role - Boehringer, Astra Zeneca, Pierre Fabre, Pfizer. N. Masuda: Personal Fees, Honoraria; Research funding -Chugai, Astra rezena, kyowa km Research funding: Pfizer, Novartis, Eli Lilly. S-A. Im: Grant - Astra Zeneca Advisory Role -AZ, Roche, Novartis. N. Harbeck; Honoraria; Amgen, Celgene; Nanotrophic Technologies; Novartis; Pfizer; Research Consulting/Advisory role - AstraZeneca, Celgene, Genomic Health, Novartis, Roche/Genentech; Sandoz, WLEX Research funding -Boehringer Ingelheim, Novartis, Pfizer;

Phase I/II trial of palbociclib in combination with bicalutamide for the treatment of androgen receptor (AR+) metastatic breast cancer (MBC): Pharmacokinetics (PK)

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Background: Emerging evidence demonstrates that the androgen-signaling pathway plays a role in BC pathogenesis and may be a valuable therapeutic target. In TBCRC011, bicalutamide (B) in patients (pts) with AR + ER/PR- MBC was well-tolerated and demonstrated a clinical benefit rate of 19% in this population (Gucalp et al. CCR 2013). Palbociclib (P) is a competitive inhibitor of CDK4/6 and has been shown to reduce growth of AR + ER/PR+ MDA-MB-435 BC cells. In postmenopausal pts with luminal ER+B MBC the addition of P to letrozole significantly improved median progression-free survival (PFS) in comparison to letrozole alone. Given the luminal signature of AR+ triple negative BC (TNBC) and the presence of intact Rb in this ERC subtype, we are testing the efficacy of B + P in pts with metastatic AR+ + TNBC. This Phase 1 study is evaluating the safety and PK of this drug combination and will establish the recommended phase II dose for further study.

Methods: Pts with AR+ (IHC ≥1%)/ER any (HER2-) MBC on central review at MSK were eligible if met following criteria: ECOG ≤2, postmenopausal, no limit to prior regimens. Pts with ER+ BC must have had 1 prior endocrine therapy. Treatment (tx): B 100 mg orally daily and P 100 mg orally daily 3 days/week on cycle 1 for the 1st dose-escalation cohort (DLT period = 28 days). Pts are evaluated for toxicity every 2-4 weeks and for response every 8 weeks. Pts 1 standard 3 x 3 design with 3 dose escalations. Plasma for PK was collected assed throughout the study.

Results: As of 5/11/16, 17 pts with AR+ MBC are enrolled. Accrual is complete to the second dose escalation cohort and the final cohort of B 150mg P 125 mg is enrolling as of May 2016. Tx has been well tolerated: the only related Grade 3 AE was neutropenia in 1 pt. No related Grade 4 or 5 AEs were observed. One SAE of Grade 3 anemia, Grade 4 hypercalcemia was related to disease progression. PK analysis is ongoing.

Conclusions: The combination of palbociclib and bicalutamide has been well tolerated with no unexpected toxicity observed. Updated safety and PK data will be presented.

Clinical trial identification: NCT02605486

Legal entity responsible for the study: MSKCC

Funding: Pfizer

Disclosure: A. Gucaplı, T.A. Traina: Research support from Medivation, Astellas, Pfizer and InnocinAll other authors have declared no conflicts of interest

The influence of old age on everolimus exposure in patients with cancer

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Background: When starting treatment with everolimus in elderly cancer patients (pts), clinicians are often concerned about everolimus related toxicity. Elderly pts frequently have comorbidities and are considered more fragile. Therefore, upfront dose reduction of everolimus to prevent toxicity is applied more readily in elderly pts. However, very limited data are available on the pharmacokinetics (PK) in elderly pts and therefore, the influence of age on everolimus PK in cancer pts is yet unknown. The objective of this study was to determine the effect of age on everolimus PK.

Methods: In two PK studies in pts with either metastatic breast cancer or advanced thyroid cancer treated with everolimus 10mg OD, everolimus PK was compared between elderly pts (age ≥70 years) and control pts (age <70 years). Blood samples were collected at steady-state PK, after 2 weeks of therapy. Blood was collected for PK assessment at 0, 1, 2, and 3 hours at 0, 1, 2, 3, 5 and 8 hours after everolimus intake. Whole blood concentrations were measured. Plasma concentrations were calculated by correcting for the individual hematocrit. Area under the concentration time curves over 24 hours after dosing (AUC0-24h) were calculated by using a two compartment population PK model with first order absorption using Nonlinear Mixed Effect modeling (NONMEM v7.2). Dose changes for each patient were recorded. Statistical analysis was done with SPSS, using an unpaired t-test.

Results: 19 elderly and 56 control pts were included. Comparative PK data are shown in table 1. Everolimus exposure in both whole blood and plasma did not differ significantly between the two groups. Dose reductions or discontinuations due to toxicity occurred in 42% of elderly and 48% of control pts (p < 0.73). Table results:
Background: Clinical evidence suggests that steroid aromatase inhibitors (SAI) lack cross resistance with non-steroidal aromatase inhibitors (nSAI). Therefore, none of SAI in advanced breast cancer (ABC) patients (pts) after disease progression on nSAI has been considered a reasonable option in several centers. Our aim is to confirm the effectiveness of using this strategy in ABC and identify predictors of response.

Methods: Retrospective analysis of a cohort of consecutive ABC female postmenopausal hormone receptor patients treated in a single cancer center with SAI (exemestane) after progression with nSAI (letrozole or anastrozole), between 2009 and 2013. Effectiveness outcomes were time to progression (TTP) and clinical benefit. The aim of the study was to validate the efficacy of using this strategy in ABC and identify predictors of response.

Results: 163 consecutive eligible pts were enrolled. Pts characteristics: median age 68 years. In univariable analysis, the factors associated with CB were visceral disease (OR 2.24 95%CI 1.1-4.58, p 0.03) and >1 site of metastases (HR 2.53 95%CI 1.54-4.22, p <0.0001) were prognostic factors for OS. Estrogen receptor level expression >50% (OR 3.49 95%CI 1.30-9.38, p 0.01), 1 metastases: 32%; ECOG PS = 1: 62%. Median of cycles administered: 14 (range 6-28).

Conclusions: Our real world experience confirms that F500 can safely be offered to most women with HR +/HER2- MBC, with interesting expectations of FPS and CB and good safety profile, producing similar outcomes as both PD treatment and maintenance therapy.

Legal entity responsible for the study: Raffaele Palumbo

Funding: IRCCS Fondazione S. Maugeri

Disclosure: All authors have declared no conflicts of interest.

**Table: 2B3P**

| Parameter | Controls (n = 56) | Elderly (n = 19) | P
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.5 (37.69)</td>
<td>73.4 (70-80)</td>
<td>.008</td>
</tr>
<tr>
<td>Whole blood AUC0-24</td>
<td>309.1 (79.3)</td>
<td>190.0 (66.3)</td>
<td>.349</td>
</tr>
<tr>
<td>Plasma AUC0-24</td>
<td>580.0 (223.1)</td>
<td>507.9 (182.3)</td>
<td>.208</td>
</tr>
</tbody>
</table>

AUC0-24 = area under concentration–time curve from zero to 24 hours, µg*h/L.

This retrospective multicenter observational study was conducted to describe the patterns of treatment and outcome of F500 in the real life setting.

Methods: Data of postmenopausal HR +/HER2- MBC pts who received F500 from January 2011 to December 2014 were collected from institutional databases of 4 Italian Centers. The primary study aim was to analyze progression-free survival (FPS) and Clinical Benefit Rate (CBR: complete response [CR] + partial response [PR] + stable disease [SD]) > 24 weeks), secondary endpoints included overall survival (OS) and safety profile.

Results: 490 pts were included in the study. 480 were evaluable. F500/month was given as 1st up to 7th treatment line: 1st line in 24% of pts, 2nd line in 35%, ≥3rd in 41%. 306 pts received the drug upon progression of disease (PD) on prior endocrine treatment, 92 and 68 as maintenance therapy following 1st or 2nd line chemotherapy, respectively; 21% of pts had de novo metastatic disease. Median age: 66 years (range 56-81), visceral metastases: 32%, ECOG PS = 1.62%. Median of cycles administered: 14 (range 6-28). At a median follow up of 18 months (range 6-38) median FPS was 11.6 months (range 8.1-16.2) in 1st line, 11.4 in ≥2nd line, 9.2 in >3rd lines), CBR was 68.6% (98% CB, 21.6 PR, 38.2 SD: 24 weeks). No differences in CBR (67.8% vs 69.1%) and FPS (11.5 vs 11.6 months) were observed between pts receiving F500 as maintenance therapy and those treated at PD on prior therapy. Median OS was 44.2 months (range 35-97). More frequent toxicities did not exceed grade 1 NCI-CTC: local injection site pain (11.2%), joint disorders (6.2%), hot flushes (4.9%).

Conclusions: Our real world experience confirms that F500 can safely be offered to most women with HR +/HER2- MBC, with interesting expectations of FPS and CBR and good safety profile, producing similar outcomes as both PD treatment and maintenance therapy.

Legal entity responsible for the study: Raffaele Palumbo

Funding: IRCCS Fondazione S. Maugeri

Disclosure: All authors have declared no conflicts of interest.

**Table: 2B3P**

**Predictors of effectiveness of the use of steroidal aromatase inhibitors after progression on non-steroidal aromatase inhibitors in advanced breast cancer patients**

M. M. Ulrich de Menezes Pereira dos Santos, C. Cardoso, M. Sousa, S. Esteves, M. Brito, A. Moreira Oncology, IPO LFG, Lisbon, Portugal

Background: Clinical evidence suggests that steroid aromatase inhibitors (SAI) lack cross resistance with non-steroidal aromatase inhibitors (nSAI). Therefore, none of SAI in advanced breast cancer (ABC) patients (pts) after disease progression on nSAI has been considered a reasonable option in several centers. Our aim is to confirm the effectiveness of using this strategy in ABC and identify predictors of response.

Methods: Retrospective analysis of a cohort of consecutive ABC female postmenopausal hormone receptor patients treated in a single cancer center with SAI (exemestane) after progression with nSAI (letrozole or anastrozole), between 2009 and 2013. Effectiveness outcomes were time to progression (TTP) and clinical benefit. The aim of the study was to validate the effectiveness of using this strategy in ABC and identify predictors of response.

Results: 160 ABC pts were identified, with a median age of 60 (range 32-87). In 74% pts estrogen receptor was high (25%) and in 16% HER2 was overexpressed. Visceral disease was present in 25% pts and 67% had been previously treated with adjuvant endocrine therapy. In ABC, 37% were initially treated with nSAI. The average number of therapeutic lines until exemestane was 2.3 (1.8) and 33% were treated with exemestane immediately after progression under nSAI. The exemestane CR rate was 64%. In univariable analysis, the factors associated with CB were visceral disease (p = 0.047), previous CB to nSAI (p = 0.047) and number of treatment lines between nSAI and exemestane (p = 0.011). In multivariable analysis, visceral disease and CB to nSAI were the only independent factors significantly associated with CB to exemestane (OR 0.38 and 2.15, respectively). The median TTP was 7.8m (95%CI 6.4-9.2). In multivariable analysis, visceral disease and the number of treatments between AI were the only independent factors significantly associated with TTP (HR 1.35 and 1.56, respectively).

Conclusions: The use of exemestane after progression on nSAI seems to be a valid option, especially in ABC patients with non-visceral disease, few treatment lines between nSAI and SAI and with previous CB to nSAI.

Legal entity responsible for the study: IPO Lisbon

Funding: IPO Lisbon

Disclosure: All authors have declared no conflicts of interest.

**2B3P**

**Patterns of treatment and outcome of fulvestrant 500mg in postmenopausal women with hormone-positive (HR +)/Her2-negative (HER2-) metastatic breast cancer (MBC): a real-life multicenter Italian experience**

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Background: Fulvestrant 500 mg (F500) is a well-established therapeutic option for HR+/HER2- MBC postmenopausal patients (pts) who had previously progressed on hormonal therapy. Available data on F500 use in routine clinical practice are lacking.

Conclusions: Everolimus PK is not affected by older age. Upfront dose adjustment, hormonal therapy. Available data on F500 use in routine clinical practice are lacking.
**Is the overall survival after hormone therapy for hormone-receptor-positive, HER2-negative metastatic breast cancer still better than for triple-negative metastatic breast cancer?**

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**Background:** Hormone-receptor-positive (HR+) HER2-negative (HER2-) metastatic breast cancer (MBC), i.e. luminal-type MBC, is known to have a better prognosis than triple-negative MBC (TNMBC). However, in HR+ HER2-MBC patients who receive RT, the difference in overall survival between patients who received RT and those who did not has not been well-documented.

**Methods:** We herein reviewed our medical records from 2002 to the present to assess the OS beyond HTx and identify the prognostic factors in HR+ HER2-MBC patients. Statistical analyses were performed using the Kaplan-Meyer method and a multivariate COX regression analysis.

**Results:** We identified 344 HR+ HER2-MBC pts from our medical records, and 286 (207 recurrent [rBC], 79 advanced [aBC]) underwent CTx. Among those 286 pts, 239 (83.6%) received at least 1 or more HTx sessions prior to CTx, while the other 47 (16.4%) received CTx as initial systemic therapy. We also extracted 95 (69 rBC, 26 aBC) TNMBC pts from the records as a control group. The median OS for the 286 pts from the diagnosis of MBC was 139.95 days (95% confidence interval [CI] 100.0–182.0) for rBC pts and 178.9 days (95% CI 149.8–208.0) for aBC pts, which was significantly longer (p < 0.01, log-rank) than that in TNMBC pts (777.0 days, 95% CI 238.0–1784.0, p < 0.001, log-rank). The median OS from the initiation of CTx was 97.2 days (95% CI 294.0–2285.0) in HR+ HER2-MBC pts, which was significantly longer (p < 0.01, log-rank) than that in TNMBC pts. However, when limited to rBC pts, who comprise the majority of HR+ HER2-MBC pts, the OS from the initiation of CTx was almost the same as that of TNBC pts (median 93.20 and 866.0, respectively, p = NS). Multiple analyses further revealed that rBC pts who had a disease-free interval (DFI) of less than 24 months or pts who had bone lesions at the initiation of CTx showed a significantly poorer prognosis than those who had a longer DFI or no bone lesions (hazard ratio of 1.56 [95% CI 1.01–2.33] and 1.97 [1.02–2.40], respectively).

**Conclusion:** Our single-institution retrospective analysis with some limitations found that the OS after HTx in recurrent HR+ HER2-BC pts was almost identical to that of recurrent TNBC pts.

Legal entity responsible for the study: Junichiro Watanabe

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Abstracts

Clinical trial identification: NCT02252887 September 26, 2014
Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center
Funding: Genentech/Roche
Disclosure: All authors have declared no conflicts of interest.

**Background:** The combination of taxanes with trastuzumab (H) and pertuzumab (P) for first line treatment of HER2-positive metastatic breast cancer (MBC) is associated with improved progression-free survival (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 common, 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 trastuzumab (G) with HP. Eligible patients had HER2-positive (IHC 3+ or FISH > 2.0) MBC with prior HP-based treatment and ≤ 3 prior chemotherapies. Patients received G (1200 mg/m²) on days 1 and 8 of a 3 week (w) cycle, and H (8 mg/kg load + 8 mg/kg maintenance) and P (840 mg load → 420 mg q3w). The primary endpoint is PFS at 3 months. Secondary endpoints include OS, safety and tolerability. An exploratory endpoint is to compare PFS by RECIST criteria versus 18-F FDG-PET response criteria. Using a Simon optimal 2-stage design, 21 patients were enrolled in stage 1. The successful 3-month PFS rate for stage 1 was set at 57% to allow accrual to stage 2 for a total of 45 patients. The study therapy will be considered successful if at least 27/45 (60%) patients are progression free at 3 months.

**Results:** As of April 11, 2016, 22 patients are enrolled, 17 are evaluable at 3 months and 5 have not had 3-month evaluation. At 3 months, 12/17 (71%) are progression free (1 CR, 4 PR, 7 SD); 3 patients have progressed. The 3-month PFS results for evaluable patients will be updated. There are no cardiac or febrile neutropenic events to date. 5 patients required G dose reduction (4 due to grade 3 neutropenia and 1 due to grade 3 vomiting) and the study was amended to lower initial G dose to 1000 mg/m².

**Conclusions:** The preliminary 3-month PFS is 71% in evaluable patients, and updated data will be presented. These findings suggest clinical benefit when P is continued beyond progression.

**Clinical trial identification:** NCT02252887 September 26, 2014
**Legal entity responsible for the study:** Memorial Sloan Kettering Cancer Center
**Funding:** Genentech/Roche
**Disclosure:** All authors have declared no conflicts of interest.

**HER2 positive breast cancer with central nervous system metastases: Pathological features and clinical outcome**

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**Background:** Since the introduction of trastuzumab-containing therapies, patients with HER2+ breast cancers (BC) are experiencing longer progression-free (PFS) and overall survival (OS). However, the increasing life expectancy is associated with an increased incidence of central nervous system (CNS) metastases. Objective of the study is the identification of potential clinicopathological features associated with CNS metastases compared to patients who develop extracranial metastases in HER2+ patients.

**Methods:** We retrospectively analyzed 232 metastatic HER2+ BC patients (ER/HER2+, n = 126; ER+/HER2+, n = 89; OS was estimated by the Kaplan-Meier method and differences between groups were assessed by the log-rank test. The incidence of CNS metastases was considered as a time depend variable. Cox proportional hazard model was used to estimate Hazard ratio (HR) with 95% confidence intervals (CI). Statistical significance was set at 0.05.

**Results:** 27/126 (21.4%) patients had CNS metastases (9.3% at first diagnosis of BC). CNS metastases were associated with improved progression-free survival (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 common, the efficacy of continuing HP-based treatment after progression on P-based therapy is unknown.

**Conclusions:** The preliminary 3-month PFS is 71% in evaluable patients, and updated data will be presented. These findings suggest clinical benefit when P is continued beyond progression.
A randomized phase II study to determine the efficacy and tolerability of two doses of eribulin plus lapatinib in trastuzumab pre-treated patients with Her2-positive metastatic breast cancer - E-Vita -


Universitätsklinikum Hamburg-Eppendorf KMTZ, Hamburg, Germany, have declared no conflicts of interest.

Disclosure: G. von Minckwitz: Institution received grant from Eisai. All other authors

Funding: Eisai

q21.

The combination of E and L show an acceptable safety profile. Due to progression.

arms due to neutropenia (47.6% vs 70.0%), fatigue (19.0% vs 0.0%) and diarrhea (9.5% vs 5.0%).

more common under E1.76. Overall the most frequently grade 3-4 AEs were

13.7-30.1]). RR was 52.4% (95% CI 31.0-73.7) vs 45.0% (95% CI 23.2-66.8). CBR was

1000mg os d1-21 (3w cycle). Treatment was given until disease progression or

time to progression (TTP), safety and overall survival (OS). It was planned to recruit a total of 80 pts.

The study was stopped in 7/2014 due to slow accrual. Median age was 54 yrs. Median

Between 2/2012 and 7/2014 43 pts were randomized (41 started treatment).

Results:

and overall survival (OS). It was planned to recruit a total of 80 pts.

compliance. Secondary endpoints were response rate (RR), clinical benefit rate (CBR)

unacceptable toxicity. Primary endpoints were time to progression (TTP), safety and
efficacy and tolerability of two doses of Eribulin plus Lapatinib in T pre-treated pts with HER2+ ABC.

E-VITA (NCT01534455) is a randomized phase II study to determine the

efficacy and tolerability of two doses of E plus L in 1 T pre-treated pts with HER2+ ABC. Main eligibility criteria were: ABC not suitable for surgery or radiotherapy alone; adjuvant and up to 3 chemotherapy regimen for ABC. Pts were randomized (1:1) to receive E 1.25mg/m2 (d 1-21) plus L 1750mg/m2 (q21) or E 1.8mg/m2 (d 1-21) plus L 1000mg or q21 (3w cycle). Treatment was given until disease progression or unacceptable toxicity. Primary endpoints were time to progression (TTP), safety and compliance. Secondary endpoints include response rate (RR), clinical benefit rate (CBR) and overall survival (OS). It was planned to recruit a total of 80 pts.

Results: Between 2/2012 and 7/2014 43 pts were randomized (41 started treatment).

The study was stopped in 7/2014 due to slow accrual. Median age was 54 yrs. Median TTP was 8.1 months (95% CI 4.8-9.4) with E1.25 vs 6.5 months (95% CI 4.6-13.4) with E1.76. No difference in OS was seen (23.1 [95% CI 12.5-35.0] vs 22.3 months [95%CI 13.7-30.1]). RR was 52.4% (95% CI 31.0-73.7) vs 45.0% (95% CI 23.2-66.8). CBR was 71.4% (95% CI 52.1-90.8) vs 75.0% (56.0-94.0). High grade adverse events (AEs) were more common under E1.76. Overall the most frequently grade 3-4 AEs were neutropenia (47.6% vs 70.0%), fatigue (19.0% vs 0.0%) and diarrhoea (9.5% vs 5.0%). 5 pts discontinued therapy due to AEs (2 in E1.25 arm and 3 in E1.76). 13 pts in both arms due to progression.

Conclusions: The combination of E and L show an acceptable safety profile. Due to premature study termination, no definitive conclusion on efficacy can be drawn. However, due to its lower toxicity profile, the preferred regimen remains E1.25 vs E1.76.

Clinical trial identification: NCT01534455

Legal entity responsible for the study: German Breast Group

Funding: Eisai

Disclosure: G. von Minckwitz: Institution received grant from Eisai. All other authors have declared no conflicts of interest.
Trastuzumab emtansine (T-DM1) in patients (pts) with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC): Results from a multicenter retrospective analysis

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Results: T-DM1 improved outcomes in pts with HER2+ MBC, but few data concerning its use in routine clinical practice are available. Methods: We retrospectively enrolled 194 HER2+ (IHC 3+ or 2+ amplified) MBC pts treated with T-DM1 in real-world practice in 20 Italian oncologic centers. Results: Baseline pts and tumors characteristics are listed in Tab 1. Median (m) follow-up was 9.8 months (mo) (range, 2-37), m T-DM1 treatment duration was 5 mo (range, 2-12). Objective response (OR) was 35% (95% CI, 27-43), partial response (PR) was 26% (95% CI, 18-34), stable disease (SD) was 9.8%, and progressive disease (PD) was 29.6%. Toxicity was recorded in 26.8% pts, with a clinical benefit (CB: response or SD lasting ≥ 3 months) in 5.6% of pts, most commonly thrombocytopenia and fatigue. Cardiac dysfunction was reported in 2 pts (1%). Conclusions: In this real-world setting of heterogeneous HER2+ MBC pts, efficacy of T-DM1 was comparable with that reported in phase II-III studies, without new safety issues.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Median (range)</td>
<td>56 (34-82)</td>
</tr>
<tr>
<td>Hystology Ductal Lobular Other</td>
<td>173 (89.2) 1 (5.7) 10 (5.1)</td>
</tr>
<tr>
<td>Grading G2 G3 Unknown (UK)</td>
<td>55 (28.4) 124 (63.9) 15 (7.7)</td>
</tr>
<tr>
<td>Metastate at diagnosis Yes No</td>
<td>47 (24.2) 147 (75.8)</td>
</tr>
<tr>
<td>HER2+ at diagnosis Yes No UK</td>
<td>157 (80.9) 25 (12.9) 12 (6.2)</td>
</tr>
<tr>
<td>ECOG PS 0 1 2 3 UK</td>
<td>97 (50) 63 (32.5) 9 (4.6) 1 (0.5) 24 (12.4)</td>
</tr>
<tr>
<td>Previous regimen for MBC 0 1 2 ≥3</td>
<td>10 (5.1) 40 (20.6) 47 (24.2) 97 (50)</td>
</tr>
</tbody>
</table>

Conclusions: In this real-world setting of heterogeneous HER2+ MBC pts, efficacy of T-DM1 was comparable with that reported in phase II-III studies, without new safety issues.

Legal entity responsible for the study: Patrizia Vici
Funding: None
Disclosure: All authors have declared no conflicts of interest.

Electrochemotherapy for breast cancer - results from the INSPECT database

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Background: Cutaneous recurrence from breast cancer can pose a clinical challenge. It may be the only disease site, or be part of disseminated disease, and often profoundly impacts quality of life. Electrochemotherapy is a palliative treatment for cutaneous metastases. Using electric pulses to locally permeabilize tumor cells, bleomycin cytotoxicity is significantly increased. Collaborating in the International Network for sharing Practice on Electrochemotherapy (INSPECT) we consecutively and prospectively accrued data on patients treated with electrochemotherapy for skin metastases of breast cancer.

Methods: Patients with cutaneous metastases were treated with electrochemotherapy at 16 European centers. Treatment data and results were entered into the INSPECT database. Patients were treated with either local injection (1000 IU/ml intratumoral injection) or systemic infusion (15.000 IU/ml) of bleomycin, and under either local or general anesthesia, depending on tumor size. Electrochemotherapy was sequentially applied to the tumor area, using an electroporation system with needle or plate electrodes (IGEA, Italy).

Results: 104 patients were included. Median age was 65 years. Patients had previous (57.6%) radiotherapy (87%), radiotherapy (83%), endocrine therapy (46%) and HER2 targeted therapy (20%). Primary location was the chest (87%), median diameter of the cutaneous metastases being 26 mm (range 11-54 mm). 73 patients were available for response evaluation after 2 months. Complete response was observed in 38 (31%) patients, partial response in 13 (17%), stable disease in 44 (19%), and progressive disease in 13 (9%), 3 patients were not evaluable. Common side effects were ulceration, long lasting hyperpigmentation, and slight increase in pain. No serious adverse events were observed.

Conclusions: Electrochemotherapy showed high response rates, particularly in smaller metastases. Electrochemotherapy has high response rates seen after a single treatment, with few side effects and can be used as an adjunct to systemic therapies as well as a sole treatment. We therefore highly recommend to consider electrochemotherapy for patients with cutaneous metastases, where radiotherapy and surgery is not an option.

Legal entity responsible for the study: Each center participating in the study are responsible for governance and running of the study, and are legally responsible for the study at their own institution. Coordination was performed by investigators at one center elected by the International Network of Sharing Practices of Electrochemotherapy, which is a collaboration of between clinicians and centers performing electrochemotherapy.

Funding: The study is funded by each center. IGEA, Carpi, Italy is funding and maintaining the database, where the INSPECT members upload data.

Disclosure: F. de Terlizzi Employee in IGEA, Carpi, Italy. All other authors have declared no conflicts of interest.
Phase 1b/2 safety and efficacy of TAK-228 (MLN0128), plus exemestane (E) or fulvestrant (F) in postmenopausal women with ER+/HER2- metastatic breast cancer (MBC)


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Disclosure: Authors have declared no conflicts of interest.

Funding: This phase 1 study of ONT-380, a potent, oral selective small molecule inhibitor of HER2, dosed in 2 cohorts of 30mg PO BID (8 pts) and 30mg PO BID (52 pts) given with either C (1000mg/m² PO BID 14 days of 21-day cycle) or T (8mg/kg IV load, then 6mg/kg IV once every 21 days) or the combination was conducted in women with HER2+ MBC previously treated with trastuzumab and T-DM1. Prior lapatinib, neratinib, and pertuzumab were allowed. Tumor response was assessed by RECIST 1.1. Sixty patients were treated on study and 27 received the triplet of ONT-380 with C and T. Eight patients had skin noted as a site of disease.

Results: Skin was a measurable site of disease in 6 women and non-measurable site in 2 women. In all 8 women there were clinical responses in the skin with ONT-380 and C (2 pts), ONT-380 with T (1 pt) or ONT-380 with C plus T (5 pts). Two women had complete response of their skin disease, 3 had partial response (PR) and 3 had PR + SD. A median time on therapy was 8.5 cycles (5–13 range). One patient is still on study.

Conclusions: We report on 8 patients with significant response in skin as a disease site while on ONT-380 with either C or T or the combination. ONT-380 shows evidence of efficacy in cutaneous metastases, a common and difficult site of disease to control for women with HER2+ MBC.

Clinical trial identification: NCT02025192

Legal entity responsible for the study: Oncothyreon Inc.

Funding: Oncothyreon Inc.

Disclosure: L.N. Walker: I am an employee of Oncothyreon, Inc.; 2S.L. Moulder: My only disclosures are to be a non-compensated advisor to Oncotarget and to have received funding to support the clinical trial including effort as PI. All other authors have declared no conflicts of interest.
adverse events and their rates in the UGT1A1 wt/wt and wt/*28 heterozygous groups were diarrhoea, 25% and 46%; vomiting, 17% and 9%; anaemia, 25% and 9%; and fatigue, 25% and 9% respectively. As shown in Table 1 and supported by PK data, PFS seemed better for the UGT1A1 wt/wt or *28 group compared to that for the wt/*28 group. There also seemed to be an association between clinical benefit and suppression of CD3+ T cells.

Table 2: 279P Efficacy results of Level 2 patients (n = 28, 6 for phase I and 22 for phase II)

<table>
<thead>
<tr>
<th></th>
<th>Wild/Wild</th>
<th>Wild/*28</th>
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<tbody>
<tr>
<td>(n = 15)</td>
<td></td>
<td>(n = 14)</td>
</tr>
<tr>
<td>Response Rate</td>
<td>1 (7%)</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>Clinical Benefit Rate</td>
<td>4 (27%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>8.3</td>
<td>12.3</td>
</tr>
<tr>
<td>(p = 0.0600)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS (month)</td>
<td>17.4</td>
<td>23.1</td>
</tr>
<tr>
<td>(p = 0.5607)</td>
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</tbody>
</table>

Conclusions: A combination of CPT and S-1 is effective in patients having recurrent/metastatic breast cancer, and further study of the underlying pharmacogenomics/PK/PD is warranted.

Clinical trial identification: UMIN00000517
Legal entity responsible for the study: Masakazu Toi

Background: S is a potent and selective oral inhibitor of Smo, a key component of the hedgehog (Hh) signaling pathway. Up-regulation of the Hh pathway is implicated in the genesis of a wide range of tumors including TN breast cancer. Here we report a phase I study exploring the combination of S with D in TN ABC pts to identify the Maximum Tolerated Dose (MTD) and Recommended Phase II Dose (RP2D) (ClinicalTrials.gov identifier: NCT02027376).

Methods: Pts with ≥3 prior chemotherapy regimens for ABC were included. Treatment consisted of 21-day cycles (cy) of D (75 mg/m² on day 1) and increasing doses of S given once daily (QD). A standard 3 + 3 design was followed including 3 dose levels (DL) for S: DL1 400mg, DL2 600mg and DL3 800mg. The primary objective was to define the MTD and RP2D of the combination based on dose-limiting toxicities (DLT) in the first 2 cy. Secondary objectives included the evaluation of safety, changes on QTC, efficacy, and pharmacokinetics (PK).

Results: 12 pts were included (3 DL1, 4 at DL2 and 3 at DL3). 3 pts were replaced due to early disease progression (PD). Median age was 49 years and 70% were female. 11 pts received a median of 2 cy (2–4) at DL1, 2 cy (1–3) at DL2 and 8 cy (6–9) at DL3. No DLTs were observed in any DL. DL3 was the MTD, and toxicities grade (G) 3, none G4, in all cytotoxicities (DLT) in the first 2 cy. Secondary objectives included the evaluation of safety, changes on QTC, efficacy, and pharmacokinetics (PK).

Conclusions: S can be safely combined with D. Co-administration of S and D seems not to have PK interaction. S 800mg QD and D 75mg/m² was declared as the RP2D.
Lines of therapy) and all except 3 previous radiotherapies. Nine patients had a PS 1, eight had a PS 2 and four had a PS 3. Eighty percent were symptomatic and sixty-five percent were taking pain killers. Patients received daily 10 mg/Kg of oral (24-ethyl-cholestane- \(3\alpha,5\alpha\),6α-tro) divided in 3 equal doses, until disease progression.

Results: Two patients exhibited a complete remission (CR). Nine patients had a partial response (PR), five patients had a stable disease (NC) and five patients had a disease progression (PD). The median duration of response was 11 months and 6 patients are still under treatment. One patient with lepto-meningeal involvement is still alive and under treatment after 49 months. No toxicity was observed so ever. Eighty percent of symptomatic patients had a remarkable symptom control.

Conclusions: These encouraging results make this new and safe drug a good candidate for further clinical trials either alone or in association with other drugs in advanced breast cancer.

Legal entity responsible for the study: Nabil Habib Institute, Beirut, Lebanon.

Funding: Nabil Habib Institute, Beirut, Lebanon.

Disclosure: All authors have declared no conflicts of interest.

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Satisfaction with cancer treatments in HR+ /HER2- metastatic breast cancer patients in a real world setting

J. de Courcy,1 R. Wood,2 D. Mitra,3 S. Iyer3

Adelphi Real World, Adelphi Group Ltd., Bollington, UK, 2Global Outcomes and Evidence, Pfizer Inc., New York, NY, USA

Background: To assess patient reported cancer treatment satisfaction in HR+/HER2- metastatic breast cancer (MBC).

Methods: Physicians were recruited into the Disease Specific Program (DSP) across 5 European countries (UK, FR, DE, ES, IT) and the US. Patients (N = 739) completed self-reported questionnaires which included the Cancer Therapy Satisfaction Questionnaire (CTSQ), this assesses 3 domains: Expectations of Therapy (ET), Feelings about Side Effects (FSE) and Satisfaction with Therapy (SWT). Each domain is scored from 0-100 with a higher score associated with the best outcome. Results are reported for the overall cohort, by current therapy and by metastatic sites. Significance was assessed using Mann-Whitney U and Kruskal-Wallis tests.

Results: A total of 611 MBC patients completed the questionnaire; mean age (SD) 66.3 (10.3). Most patients received either chemotherapy w/o endocrine therapy (46.2%) or chemotherapy therapy w/o chemotherapy (48.8%). 5.1% received both or neither. Mean scores (SD) for ET, FSE and SWT were 60.6 (21.0), 54.9 (17.5) and 69.9 (15.4) respectively. Domain scores are stratified by current therapy and metastatic sites in Table 1. ET scores did not vary by either stratification. Significantly worse scores were reported in the chemotherapy group for the FSE and SWT domains, while bone and visceral metastases patients reported worse FSE outcomes. When stratified by therapy, patients with bone and visceral metastases scored lower on most domains compared to other metastases groups (not significant).

Conclusions: Therapy expectations do not differ by therapy type or metastatic sites. Patients on chemotherapy appear less satisfied with their treatment and feel worse about their side effects than patients on endocrine therapy. Presence of bone and visceral metastases is associated with worse feelings about side effects.

Legal entity responsible for the study: Adelphi Real World.

Funding: Pfizer


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Patient reported pain severity and interference in HR+/HER2- advanced/metastatic breast cancer in real world settings

R. Wood1, J. de Courcy1, D. Mitra2, S. Iyer3

1Adelphi Real World, Adelphi Group Ltd., Bollington, UK, 2Global Outcomes and Evidence, Pfizer Inc., New York, NY, USA

Background: To assess patient reported pain severity and pain interference in HR+/HER2- advanced/metastatic breast cancer (ABC/MBC) across multiple countries in a real world setting.

Methods: Physicians across 5 major EU countries and the US participated in a cross-sectional study of over 2000 patients with HR+/HER2- ABC/MBC. A subset of patients (N = 739) completed validated questionnaires, including the Brief Pain Inventory (BPI), used to assess the severity and impact of pain on daily functions. Pain severity is reported at its worst on a 0-10 scale, while average pain severity is a mean of 4 items on a 0-10 scale (worst & least in past 24 hours, average and current pain). On both scales a higher score implies greater pain interference. Mean scores are reported for the overall cohort and by sites of metastases and compared using Mann-Whitney U and Kruskal-Wallis tests.

Results: Mean (SD) scores for worst pain was 3.1 (2.4), average pain was 2.4 (1.9), and pain interference was 2.8 (2.2). The subgroup with bone and visceral metastases had significantly higher (p < 0.05) average pain severity (3.9 (2.9), compared to those with bone disease (no visceral metastases) (2.5 (1.9)) and those with visceral (no bone) disease (2.2 (1.9)). Pain interference was significantly higher (p < 0.05) for those with both bone and visceral metastases (3.4 (2.2)) followed by bone disease (2.9 (2.1)) and visceral disease (2.6 (2.2)). In a subset of patients receiving chemotherapy at the time of completion of the BPI, worst pain was significantly (p < 0.05) higher in patients with both metastases (3.8 (2.4)), compared to those with bone metastases (3.4 (2.3)) and those with visceral metastases (2.8 (2.3)). No significant difference in pain interference scores were observed by type of metastatic site within the subset of patients treated with chemotherapy.

Conclusions: Low to moderate levels of pain severity and pain interference scores observed in advanced/metastatic breast cancer patients in the real world, which vary significantly by extent and site of metastases.

Legal entity responsible for the study: Adelphi Real World.

Funding: Pfizer


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Association of age and body mass index with paclitaxel-induced peripheral neuropathy in patients with breast cancer

Z. Ghoreishi1, A. Esfahani2, S. Keshavarz2

1Nutrition Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, 2Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, 3School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

Background: Peripheral neuropathy is one of the most common dose-limiting side effects of paclitaxel in patients with breast cancer. This study investigated the association of age and body mass index (BMI) with incidence and severity of paclitaxel-induced peripheral neuropathy (PPIP) in these patients.

Methods: Analyzed data belonged to a randomized double-blind placebo controlled trial (ID registration at ClinicalTrials.gov: NCT01049295) in which the effect of n-3 polyunsaturated fats (PUFAs) on PPIP in patients with breast cancer was examined. Logistic regression analysis (estimation odds ratio) and ordinal regression analysis were used for finding the association of age and BMI with incidence and severity of PPIP (adjusting for intervention effect) respectively.

Results: Age was associated with PPIP in 57 patients with breast cancer (mean age and BMI: 45.97± 10.75 and 45.16± 8.93, respectively) such that for every one-year increase in age, incidence and severity will increase 8% and 7% respectively (OR = 1.08, 95% CI (1.01 to 1.14)), compared to those with bone disease (no visceral metastases) (2.5 (1.9)) and those with visceral (no bone) disease (2.2 (1.9)). Pain interference was significantly higher (p < 0.05) for those with both bone and visceral metastases (3.4 (2.2)) followed by bone disease (2.9 (2.1)) and visceral disease (2.6 (2.2)). In a subset of patients receiving chemotherapy at the time of completion of the BPI, worst pain was significantly (p < 0.05) higher in patients with both metastases (3.8 (2.4)), compared to those with bone metastases (3.4 (2.3)) and those with visceral metastases (2.8 (2.3)). No significant difference in pain interference scores were observed by type of metastatic site within the subset of patients treated with chemotherapy.

Conclusions: Low to moderate levels of pain severity and pain interference scores observed in advanced/metastatic breast cancer patients in the real world, which vary significantly by extent and site of metastases.

Legal entity responsible for the study: Adelphi Real World.

Funding: Pfizer

First-line cobimetinib (C) + paclitaxel (P) in patients (pts) with advanced triple-negative breast cancer (TNBC): Updated results and tumoral immune infiltration data from the phase 2 COLET study


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Background: Resistance to standard taxane-based chemotherapy is common in TNBC. Preclinical data suggest that MEK inhibition may overcome taxane resistance and enhance antitumor immune response. The safety and efficacy of combining C, a highly selective MEK inhibitor, with P was explored in pts with metastatic/local advanced TNBC and no prior systemic therapy for metastatic disease.

Methods: The COLET study (NCT02322834; EudraCT number, 2014-002230-32) consisted of a safety run-in (n = 121) followed by a blinded 1:1 randomised stage (n = 100 pts) to C + P or placebo (PBO) + P. Pts were treated with P 80 mg/m² on days 1, 8, and 15 and C/PBO 60 mg/d on days 3-23 of each 28-d cycle. Gene expression and C/T cell infiltration were measured by RNA-Seq and immunohistochemistry, respectively.

Results: Sixteen women (median age, 55.5 years) were enrolled in the safety stage. At data snapshot (April 22, 2016), all 16 pts had received ≥1 dose of study treatment. Median time on treatment was 116 d (range, 7-336) for C and 84 d (range, 0-351) for PBO. Pts had ≥1 grade 3 AEs of alopecia (n = 4), neutropenia (n = 4), and diarrhea (n = 6). ≥3 grade 3 AEs included: alopecia (n = 1), neutropenia (n = 1), diarrhea (n = 4), and nausea (n = 1).

Conclusion: This is the first study to evaluate C + P in TNBC. The safety profile of C + P is consistent with that of known safety profiles. Efficacy and safety will be further evaluated in the ongoing randomized stage.

Clinical trial identification: ClinicalTrials.gov ID NCT02322834; EudraCT number, 2014-002230-32.

Legal entity responsible for the study: Hoffmann-La Roche, Ltd.

Funding: This study was funded by Hoffmann-La Roche, Ltd.


Mutation screening and clinical evaluation of multiple-gene sequencing for triple negative breast cancer

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Background: Triple negative breast cancers (TNBCs) were proved to be a heterogeneous disease with a wide spectrum of genomic alterations. TNBC is associated with early recurrence of disease and poor outcome. Recently next generation sequencing (NGS) is entering practice, whether multiple-gene changes have some relevance with TNBC, whether predict heterogeneity, prognostic or chemosensitivity of TNBC patients are worthy to be explored.

Methods: 170 TNBC patients were invited to donate a research blood sample, including 100 patients unselected for family history of breast cancer and 70 patients with neo-adjuvant chemotherapy. For each patient, genomic DNA was extracted from peripheral-blood samples. NGS were used to sequence 115 genes that had cancer risk associations. Medical records were collected and patients were followed up.

Results: Overall, 36 deleterious mutations were identified in 34 patients (20%). Of these, 94% had pathogenic mutations in the BRCA1 (5.9%) and BRCA2 (3.5%) genes in 170 patients. Twenty pathogenic variants were detected in other genes except for BRCA1/2 mutations, for a prevalence of 11.8%. The affected genes were PALB2 (2.9%), ATM (1.8%), MUTHY1 (1.8%), BRIP1, CHEK2, GALNT12, HMIMR, MSRI, NTRK1, RAD90, SDHC, VHL (0/16 cases). A total of 154 variants of uncertain significance (VUS) were identified in 115 genes among 170 participants. Participants carried an average of 1.6 VUS among 49 genes. Multiple-gene analysis suggests that TNBC patient with a pathogenic germline gene mutation and/or has multiple-gene mutations has a poor outcome, however, neo-adjuvant chemotherapy is more sensitive in these patients.

Conclusion: Pathogenic mutations associated with cancer or DNA repair pathways are present at high frequency in patients with TNBC unselected for family history of cancer. VUS is prevalent in TNBCs. TNBC patients with a high level of genomic instability have a relatively poor prognosis, however, sensitive to chemotherapy. Since, additional studies are required to determine whether neo-adjuvant chemotherapy can improve survival of this group of TNBCs. These results suggest that multiple-gene sequencing may benefit TNBC patients.

Legal entity responsible for the study: Jia Zhang

Funding: National Science and Technology Support Program (No. 2015BAJ12B15)

Disclosure: All authors have declared no conflicts of interest.
receiving docetaxel as NACT. To determine the effect of these SNPs on plasma levels of docetaxel.

**Methods:** Tumour response to docetaxel was evaluated in 129 LABC patients, out of which plasma levels of docetaxel were estimated by LCMS/MS.

**Results:** Patients with "CT/TT" genotypes (response rate: 66%) of ABCB1 gene (C1236T) showed better tumor response than those with "CC" genotype (response rate: 13%) [OR = 2.94 (CI 1.15 - 7.52); p = 0.032]. The superior response in "CT/TT" genotypes can be attributed to the presence of "T" allele causing altered function of ABCB1 gene coding for MDR1 transporter. Plasma levels of docetaxel were also in line with the tumor response in "CT/TT" genotypes of ABCB1 gene (C1236T). Mean of the plasma concentration ratios (C₀/C₅₀) of docetaxel in "CT/TT" genotypes (13.49 ± 6.48 ng/mL) were significantly higher than those of the "CC" genotype (8.19 ± 3.10 ng/mL) [p = 0.003]. In contrast, the genotypes of C3435T in ABCB1 gene were not found to significantly influence the tumor response or the plasma levels of docetaxel.

**Conclusions:** These results suggest that ABCB1 C1236T polymorphism could significantly influence the treatment response to docetaxel and the plasma levels of docetaxel. Hence, our study emphasizes the importance of ABCB1 genotyping for individualization of docetaxel pharmacotherapy in breast cancer patients.

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**Table 1**: Clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54 ± 13</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28.7%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10.3%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>21.8%</td>
</tr>
<tr>
<td>Smoking</td>
<td>22.9%</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>0%</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0%</td>
</tr>
<tr>
<td>Family history of cardiovascular disease</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Conclusions:** Decrease in LVEF, related to adjuvant CT, is correlated with an increase of congestive heart failure associated miRNA. Also, there was an increase of troponin levels after last CT cycle and variations in miRNA expression levels. Among them we found a strong correlation between the decrease in LVEF and the increase in miRNA 208a in serum of patients during CT. Further studies must be performed to evaluate the impact of these observations in the cardiotoxic process.

**Legal entity responsible for the study:** Hospital Universitario y Politécnico La Fe.

**Funding:** Supported by EC grant FP7-HEALTH-2013-INNOVATION-1. Cofunded by FEDER “una manera de hacer Europa.

**Disclosure:** All authors have declared no conflicts of interest.
(dNLR) is easily accessible and simple prognostic parameter of systemic inflammation associated with breast cancer. Data regarding the dNLR in breast cancer are limited in India. We assessed dNLR as a prognostic marker in patients with non-metastatic breast cancer treated at a tertiary care institute in North India

**Methods:** We retrospectively evaluated the impact of baseline peripheral neutrophil and lymphocyte counts on survival, and investigated the correlation between inflammatory biomarkers and clinico-pathological factors in 497 consecutively treated non-metastatic breast cancer patients between 2011-2014.

**Results:**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>47(23-85)</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Lump &gt; pain &gt; ulcer &gt; bleeding</td>
</tr>
<tr>
<td>Duration of symptoms in month</td>
<td>7.8 (1-72)</td>
</tr>
<tr>
<td>Stage</td>
<td>11(14.8%), 112(46.6%), 35(34.5%)</td>
</tr>
<tr>
<td>Histology</td>
<td>Ductal 485(97.5%), Lobular 7(1.5%), Metaplastic 3(1%)</td>
</tr>
<tr>
<td>Receptor Status</td>
<td>ER+PR+HER2+ 209(42%), ER+PR+HER2+ + + 85(17%), ER-PR-HER2+ + + 71 (14%), TNBC 132(27%)</td>
</tr>
<tr>
<td>Hemoglobin in g/L</td>
<td>11.4(7-16)</td>
</tr>
<tr>
<td>Total Leukocyte count in mm3</td>
<td>7369 (2450-21900)</td>
</tr>
<tr>
<td>Absolute Neutrophil Count in mm3</td>
<td>608(1100-8800)</td>
</tr>
<tr>
<td>Elevated dNLR</td>
<td>142(28.6%)</td>
</tr>
<tr>
<td>Noodosuppression Therapy</td>
<td>117(23.5%)</td>
</tr>
</tbody>
</table>

Out of the 497 patients, with a median follow up of 33.5 months, the median disease free survival (DFS) was 33.1 months and 3-year estimated overall survival (OS) was 90%.

**Conclusions:** In patients with breast cancer, inflammatory biomarker like elevated dNLR is strongly associated with poor overall survival. It can be utilized as a readily available and reproducible prognostic factor for patients with non-metastatic breast cancer across subgroups and its integration into patient evaluation is relevant in resource limited countries like India.

**Legal entity responsible for the study:** Ethics Committee, All India Institute of Medical Science

**Funding:** All India Institute of Medical Science

**Disclosure:** All authors have declared no conflicts of interest.

We identified recurrent somatic mutations in TP53, PIK3CA, FAT1, and MLL2, and detected somatic copy number variations in ERBB2, CDK12, and MYC. Notably, we found out higher somatic mutation rates harboring in PIK3CA (66.7%) compared to TCGA and previous studies. Clinical responder and non-responder showed 61.5% and 75.0% of PIK3CA mutation rate, respectively. Interestingly, 2 patients who showed definite progression during neoadjuvant (n=1) or preoperative PIK3CA mutation (n=1) (p = 0.533), and one of them eventually died. Accordingly, survival analysis showed a consistent trend of longer survivals in patient without PIK3CA mutation, although it did not reach statistical significance.

**Conclusions:** Activating mutations in PIK3CA were abundantly found in postmenopausal ER+HER2+ breast cancer in our cohort. We carefully speculate that they might confer resistance to anti-HER-2 treatment combined with hormone therapy in neoadjuvant setting, and benefit of adding PIK3 inhibitor should be considered in this subtype.

**Clinical trial identification:** NCT 01275859

**Legal entity responsible for the study** N/A

**Funding:** N/A

**Disclosure:** All authors have declared no conflicts of interest.

Background: The addition of trastuzumab (TH) to primary chemotherapy in HER2-positive breast cancer (BC) significantly improved pathological complete response (pCR) and survival. Concurrent use of TH to an anthracycline taxane-based regimen increased pCR but raised concerns about cardiac toxicity. Given the lower cardiotoxicity of liposomal doxorubicin hydrochloride (MYOCET®), the objective of this study was to explore the benefit of liposomal doxorubicin hydrochloride plus TH in a neoadjuvant scenario.

**Methods:** Patients with stage II-III HER2-positive BC were randomized to liposomal doxorubicin hydrochloride (60 mg/m²) plus cyclophosphamide (600 mg/m²) and TH (MCH) or conventional doxorubicin plus cyclophosphamide alone (AC). The primary objective of this trial, carried out in 21 European centers, was efficacy assessed by BC-pCR; secondary objectives included pCR by hormonal status and disease stage, progression-free survival (PFS) at 5 years, and safety.

**Results:** From Mar 2008-Oct 2010, 126 patients were enrolled and were evaluable. No statistically significant differences were observed in demographics and baseline clinical characteristics between treatment groups. Adverse events and discontinuations during cycles 1-8 were similar in both treatment groups. pCR was 41.3% for the MCH group and 54.0% for the AC group but differences were not statistically significant (p = 0.154, 95% CI = −0.30 to 0.05). However, in patients with stage II disease, pCR was 31.0% vs 62.5% in favor of AC (p = 0.004, 95% CI 0.52-0.81) and TH. The primary objective of this trial, carried out in 21 European centers, was efficacy assessed by BC-pCR; secondary objectives included pCR by hormonal status and disease stage, progression-free survival (PFS) at 5 years, and safety.

**Conclusions:** MCH was similar in efficacy to the traditional regimen of AC in terms of pCR in HER2-positive BC. However in stage II patients alone, the AC arm had a
According to the national guidelines, neoadjuvant chemotherapy (NAC) is increasingly being used for downsizing the tumour in order to enable breast conservation therapy (BCT). Furthermore, NAC is indicated for patients with locally advanced breast cancer (LABC). The molecular classification of breast cancer differentiates, at least, three subgroups of tumors: the luminal subtype with cells expressing estrogen receptors and ER-related genes, the human epidermal growth factor receptor 2 (HER2)-overexpressing subtype, and the basal subtype associated with the expression of basal cell markers. 

**Background:** Breast cancer is a heterogeneous disease with different clinical behavior. The molecular classification of breast cancer differentiates, at least, three subgroups of tumors: the luminal subtype with cells expressing estrogen receptors and ER-related genes, the human epidermal growth factor receptor 2 (HER2)-overexpressing subtype, and the basal subtype associated with the expression of basal cell markers. Targeted therapies for TNBC are not completely validated and the main treatment for this group of tumors is the use of chemotherapy, including platinum as single agent or in combination with other chemotherapy agents.

**Methods:** From June 2010 to November 2011, 149 locally advanced triple negative breast cancer patients in the oncology department, Tanta University, were assigned to receive four cycles of PCb with dose of paclitaxel 80 mg/m2 and carboplatin AUC 2 given day 1 and 15 of every 4 weeks. Immunohistochemistry of the following molecular markers: the estrogen receptor, progesterone receptor, HER2, p53, and Ki67. For ERCC1, grading was (0: no expression, 1: weak expression, 2: moderate expression, 3: strong expression). Operable disease should be subjected to surgery within 4 weeks from the last chemotherapy cycle. An additional two cycles of weekly PCb were delivered after surgery in patients who achieved pCR. Four cycles PCb could be administered after surgery in patients showing response at pathologic assessment.

**Results:** Ninety patients (60.4%) showed negative ERCC1 expression. Negative ERCC1 expression was associated with higher pathological CR (71.1%) than positive ERCC1 (51.4%), respectively (p = 0.001). Five year OS was better in negative ERCC1 versus positive ERCC1 (92.1% versus 51.4% respectively, p value 0.001). Five year DFS was better in negative ERCC1 versus positive ERCC1 (69.6% versus 46.4% respectively, p value 0.001). In multivariate analysis ERCC1 maintained statistical significance as regard OS and DFS.

**Conclusions:** In conclusion, the expression of this ERCC1 protein is lower in TNBC and associated with high pathological complete response to carboplatin-taxol with better overall survival and DFS. ERCC1 and other pathological markers may be used to define better treatment lines for locally advanced triple negative breast cancer.

**Legal entity responsible for the study:** Tanta University Hospital, Oncology Department

**Funding:** The authors of the study have no conflicts of interest.

**Results:** Questionnaires were sent to 580 specialists and 140 (24%) responded, with a surgeon/medical-oncologist ratio of 50:50. LABC was the most often selected reason for recommending NAC (94%), followed by tumor downstaging to provide BCT (87%) and a strong indication for adjuvant chemotherapy (64%). Another common reason mentioned was the time span for testing on hereditary breast cancer (34%) that could be created. The most important concern for recommending NAC was the performance status (44%). Age did not play a very large role against recommending NAC (23%). Of all the respondents, 34% reported that patients where chemotherapy is recommended are not always informed about the opinion of NAC. Subanalysis for the type of hospital (academic vs teaching vs general) where the questioned specialist worked, did not play any significant role in the reason(s) to decide for NAC.

**Legal entity responsible for the study:** N/A

**Funding:** grant from the KWF (Dutch Cancer Society (DCS))

**Disclosure:** All authors have declared no conflicts of interest.

**Conclusions:** According to the national NABON Breast Cancer Audit (NBCA) there is a large variation in the use of NAC. The results of the survey give interesting insights, but could not define specific factors influencing this variation. A discrepancy is seen between the expert opinion and the actual implementation of NAC.

**Legal entity responsible for the study:** N/A

**Funding:** grant from the KWF (Dutch Cancer Society (DCS))

**Disclosure:** All authors have declared no conflicts of interest.

**Results:** From December 2012 to December 2014, we enrolled 66 patients, of whom 57 patients completed 12 cycles of nab-PTX treatment. The dose of nab-PTX was reduced 20% in 20 patients. Among all, 55 patients (83.3%) had hormone receptor-positive tumors and 11 patients (16.7%) had triple negative tumors. The response rate in the breast after nab-PTX regimen was 59.1% (95% CI, 47.2% to 71.0%). 63.6% in hormone receptor-positive tumor and 36.4% in triple negative tumor respectively (p = 0.090). The pathological complete response at the time of surgery was 15% (95% CI, 6.1% to 24.8%). Toxicity analysis showed that the incidence of grade 2 peripheral sensory neuropathy was 38 (57.6%), grade 2 or grade 3 leukopenia was 29 (43.9%), grade 2 or grade 3 neutropenia was 20 (30.4%) and grade 2 or grade 3 liver dysfunction was 5 (7.5%). Younger age, high Ki67 and low AR in IHC showed a statistically significantly higher tumor reduction rates in the breast. Low SPARC and high TOPO IIs in mRNA levels showed statistically significantly higher tumor reduction rates in the breast.

**Conclusions:** Weekly nab-PTX in the neoadjuvant setting was well tolerated, especially in the peripheral sensory neuropathy profile. Biomarker analysis suggested that high Ki67, low AR in IHC, low SPARC and high TOPO IIs in mRNA levels predict responses of weekly nab-PTX.

**Clinical trial identification:** UMIN000009526

**Legal entity responsible for the study:** Toho University Medical Center Ohashi Hospital

**Funding:** National Hospital Organization and Taiho Pharmaceutical Co.

**Disclosure:** A. Nagayama: owns stock options of Chugai, Inc.A. Matsui: received from research grants from Taiho, Takeda, Chugai, Eisai and Daiichi-Sankyo. Received lecture fees Taiho, Eisai, Kyowa-Kirin, Chugai and Daiichi-Sankyo. Y. Okamoto: received research funding from Taiho and lecture fees from Taiho, Eisai. Young age, high Ki67 and low AR in IHC showed a statistically significantly higher tumor reduction rates in the breast.
High-dose chemotherapy for inflammatory breast cancer: impact of immunohistochemical status on survival outcome

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Background: Studies examining high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HD–ASCT) strategies in inflammatory breast cancer (IBC), showed encouraging results in terms of disease-free survival (DFS), and overall survival (OS). The lack of data regarding HER2 status in all of these studies prevented any prognostic analysis involving breast cancer subtypes.

Methods: All consecutive female patients treated for IBC with HD and ASCT at Institut Paoli-Calmettes between 2003 and 2012 were included. Since 2005, trastuzumab was included in initial treatment. Patient, tumor and treatment characteristics were collected. Patients were categorized in three subtypes based on hormonal receptor (HR) and HER2 status of the primary tumor: Luminal, (HR+ / HER2-), HER2+, or mixed (HR-/ HER2+). The main objective was the analysis of OS according to the IBC subtypes.

Results: Sixty-seven patients were included. Eleven patients received trastuzumab. Median follow up was 80.40 months (95% CI 73.2-88.08). Five-year OS and DFS for the whole population patients were 74% (95% CI 61-86) and 63% (95% CI 52-76), respectively. OS differed across subtypes (p = 0.057). HR2 subgroup appeared to have the best prognosis with a 5-year OS of 89% (95% CI 64-97) compared to 57% (95% CI 44.7-65.6). Also there is significant difference (P value >0.001) in five years survival rate in T3 stage between patient who not received neither RT nor SLNB and patient who received RT and SLNB.

Conclusions: The NAC nomogram was developed to predict the likelihood of NSLN metastases (P < 0.05). The NAC nomogram was validated in an external patient cohort with AUC of 0.705. In internal cross validation, the area under the curve (AUC) was 0.791 for the NAC nomogram. In internal cross validation, the area under the curve (AUC) was 0.791 for the NAC nomogram. The obtained data indicate a direct correlation between CNV frequency alteration during NAC and tumor response to therapy (R = 0.71). We showed that the number of cytokbands bearing mosaics CNV was decreased after chemotherapy in 42% patients (13/30).

Methods: Breast cancer patients (n = 30) with stage IIIA to IIIB received four cycles of systemic anthracycline-based NAC. To study CNVs in pre- and post-NAC tumor tissues microarray analysis was performed using the Amyblossom (USA) CytoScan HD Array.

Results: The obtained data indicate a direct correlation between CNV frequency alteration during NAC and tumor response to therapy (R = 0.71). We showed that the number of cytokbands bearing mosaics CNV was decreased after chemotherapy in 42% patients (13/30). The result showed that there is significant difference (P value >0.001) in five years survival rate in T3 stage between patient who not received neither RT nor SLNB and patient who received RT and SLNB.

Conclusions: The NAC nomogram was developed to predict the likelihood of NSLN metastases (P < 0.05). The NAC nomogram was validated in an external patient cohort with AUC of 0.705. In internal cross validation, the area under the curve (AUC) was 0.791 for the NAC nomogram. In internal cross validation, the area under the curve (AUC) was 0.791 for the NAC nomogram. The obtained data indicate a direct correlation between CNV frequency alteration during NAC and tumor response to therapy (R = 0.71). We showed that the number of cytokbands bearing mosaics CNV was decreased after chemotherapy in 42% patients (13/30).

Conclusion: Our study results demonstrate that the clonal evolution of tumors under chemotherapy in breast cancer is a complex process which includes the selection of drug-resistant subclones. The result showed that there is significant difference (P value >0.001) in five years relative survival rate in T3 stage between patient who not received neither RT nor SLNB and patient who received RT and SLNB.
Breast cancer patients with metabolic syndrome have a higher clinical and pathological response to neoadjuvant chemotherapy (NACT) post neoadjuvant chemotherapy (NCCH).

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Background: Obesity was reported as a poor prognostic factor for breast cancer. There is growing evidence of increasing prevalence of obesity among Saudi women (>44%). Since the prognostic significance of obesity was not studied in Saudi patients with breast cancer the aim of this study was to evaluate the impact of BMI on pCR in LABC patients post NCCH.

Methods: Between May 2005 and July 2010, 246 consecutive patients with LABC from three tertiary care centers, (KKKHUH, Riyadh, Saudi Arabia) were included in the study. All patients had received NCth (Anthracycline based + Taxane based combination chemotherapy). Patients were categorized as normal (BMI <25 kg/m2), overweight (BMI of 25 to < 30 kg/m2) and obese (BMI >30 kg/m2) pCR was defined as no invasive cancer in the breast or axillary tissues. Univariate and multivariate analysis were used to evaluate the statistical associations between, pCR and BMI with respect to the other previously established prognostic factors.

Results: The median age was 50y (range 24-88), Male subtypes were as follows: luminal A 23.2%, luminal B 45.1%, triple negative 16.7%, Her-2 neu positive 15%, lightly six (35 %) were stage II and 160 (65 %) were stage III. Intermediate and high grade malignancy were found in 52% and 44.3% of the patients respectively. Positive lymphovascular invasion was detected in 41.5% Obese patients constitutes 55.7% of our cohort Pathologic complete response was achieved in 62 patients (25.2%). In Univariate analysis E VI and overweight (obesity were negatively correlated with pCR (P = 0.037 and 0.000 respectively) while tumor grade was positively correlated (P = 0.008). In multivariate analysis, overweight (obesity was the only significant independent factor correlating with pCR (P = 0.000).

Conclusions: In this study, overweight / obesity (which represent more than half of the patients =55.7%) had a negative impact on pCR in Saudi patients with LABC treated with NCth. This poorer outcome in overweight / obese patients necessitates further prospective studies of this risk factor in order to optimize the care of this group of patients.

Legal entity responsible for the study: King Khalid University Hospital

Funding: King Khalid University Hospital

Disclosure: All authors have declared no conflicts of interest.

Metformin in breast cancer: Surgery type as a new prognostic factor

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Background: The aim of this prospective randomized trial was the influence of metformin on the effectiveness of neoadjuvant systemic anticytotic therapy (NAST) breast cancer in patients with metabolic syndrome (MS).

Methods: The study included 54 patients (aged 46 to 77 years) who received neoadjuvant systemic treatment for stage II-III breast cancer, in the clinic of oncology National medical university named after O.O. Bogomolets in Kiev municipal clinic oncological centre between 2010-2014. All patients was diagnosed MS according to the IDF criteria and were compared by 2 groups group 1 included 36 patients with MS and BC who did not take metformin during NAST, and group 2 - 18 metabolic syndrome patients with breast cancer taking metformin with NAST. Clinical and pathological response rates were compared between the two groups using the fourfold tables analysis method.

Results: Clinical complete response (CR) was identified in 6/patients from group 1 and in 28/patients from group 2. Clinical benefit response of treatment (CR + PR) was achieved in 67% of patients treated with metformin compared to 25% patients from group 1. In 53% of patients who were not taking metformin was observed stable disease (SD). The rate of pathological complete response (pCR) was 31% in the metformin group and 6% in the nonmetformin group.

Conclusions: The addition of metformin and neoadjuvant systemic anticytotic therapy breast cancer patients with metabolic syndrome have a higher clinical and pathological CR rate and clinical benefit response of treatment than BC patient with MS not receiving metformin. This study demonstrated the potential of metformin as an antitumor agent in breast cancer patients with metabolic syndrome.

Legal entity responsible for the study: Liubota Roman

Funding: NMU named after O.O. Bogomolets

Disclosure: All authors have declared no conflicts of interest.

A multicenter study of the impact of body mass index (BMI) on the incidence of pathologic complete response (pCR) among Saudi patients with locally advanced breast cancer (LABC) post neoadjuvant chemotherapy (NCCh)

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Background: Breast cancer is the most frequently diagnosed malignancy and is a leading cause of cancer death in women worldwide. Neoadjuvant chemotherapy for breast cancer has been established as an effective therapeutic approach for advanced non metastatic breast cancer. Metformin, an oral hypoglycemic drug with well-established side effect and safety profiles, has been widely studied for its antitumor activities in a number of cancers, including breast cancer.

Methods: This study included 76 female non-diabetic patients with IDC who were eligible for neoadjuvant chemotherapy. They underwent clinical examination, bilateral mammography and ultrasound, and other standard radiologic modalities and they received anthracycline-based regimen (with or without Taxanes according to clinical response) with metformin 500mg, twice daily till time of surgery. After surgery, pathological response (by both Miller and Satellof grading systems) and RNA expression levels of p53 pathway, and the PI3K/akt/m-TOR pathway were done on tissues.

Results: The mean age was 44.3 years. The mean BMI was 32.8 Kg/m2 and 37.3 Kg/m2 in good responders and poor responders respectively (p value 0.042). Significant overexpression of AMPK, LKB1, TSC1/2, OCT1, PKA, APAF1, P53, PI3, P21, RPS6, PIDD,FADD and CHEK1/2 and reduced expression of m-TOR, CYCLIN D-1,VEGF, CDK-4, CDK-1,IGF, NFKB and AKT among responders suggesting action of metformin can be through AMPK activation and subsequent stimulation of p53, inhibition of mTOR, reduced expression of IGF1, stimulation of apoptotic pathways.

Conclusions: Obese group of patients had significantly better DFS when compared to normal-overweight group of patients, this could be explained by adding Metformin to neoadjuvant chemotherapy but further studies with larger number of patients and longer follow up is warranted. Also further efforts are needed for establishing antineoplastic molecular pathway for metformin.

Legal entity responsible for the study: National Cancer Institute, Egypt

Funding: National Cancer Institute, Egypt

Disclosure: All authors have declared no conflicts of interest.

Prognostic factors after neoadjuvant chemotherapy in breast cancer: Surgery type as a new prognostic factor

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Background: Pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) is not necessarily linked to long-term survival. Response to chemotherapy and outcomes after NAC differ among breast cancer subtypes, so we analyzed prognostic factors by subtype.

Methods: We retrospectively analyzed 451 patients treated with anthracycline and taxane-based NAC between 2007 and 2015. Trastuzumab was added for human epidermal growth factor receptor (HER)-2-positive breast cancer. pCR was defined as no residual invasive breast carcinoma; noninvasive residuals and infiltrated lymph nodes were allowed. Kaplan–Meier and multivariate cox regression analyses were used to evaluate disease-free interval (DFI) and DFI prognostic values, respectively.

Results: Median follow-up was 43 months; median age was 56 (range, 23–80) years. pCR rate was 26.2% (118/451) in all cases: 9% (8/82), luminal A, 10.9% (41/38), luminal B HER2 (--), 43.1% (31/71), luminal B HER2 (+); 59.4% (38/64), HER2; and 34% (36/106), triple negative (TN). For all subtypes, patients who achieved pCR had a non-significantly higher DFI. Multivariate Cox regression showed these associations with DFI: surgery type and Ki-67 > 30% after NAC for all cases and luminal B HER2 (--), ypN (lymph node status after NAC), luminal B HER2 (+), and menopausal status, HER2, and pCR rate, and clinical lymph node status, TN. Kaplan–Meier analysis showed that surgery type was strongly associated with DFI after NAC.

Mastectomy patients had significantly poorer prognosis than partial mastectomy patients for all subtypes except HER2. For all subtypes, the median DFI in mastectomy patients was 73 months, but DFI was not reached in partial mastectomy patients (p = 0.0001). Compared with partial mastectomy patients, mastectomy patients had a significantly shorter median DFS (hazard ratio, 1.89; 95% CI, 1.35-2.65; p = 0.0001).
more advanced disease in terms of tumor size, lymph node status, and stage and showed lesser clinical and pathological responses to NAC and effects on 4pYN.

Furthermore, first recurrences in mastectomy patients were often distant metastases, leading to poor prognosis.

Conclusion: Prognostic factors after NAC differ among subtypes. Surgery type was strongly associated with outcomes after NAC, so it could be an independent prognostic factor.

Legal entity responsible for the study: N/A

Funding: Hiroshima City Hiroshima Citizens Hospital

Disclosure: All authors have declared no conflicts of interest.

**Abstracts**

**Association between physical activity, psychological mood profile and self-esteem among breast cancer survivors**

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Background: Physical activity is defined as any bodily movement that is performed on a repeated basis with the intention of improving health or performance. Research demonstrates beneficial effects of Physical Activity (PA) and exercise among breast cancer survivors before and after treatment on psychologic outcomes, mood profile and self-esteem.

Methods: The aim of the study was to investigate the relationship between Physical Activity, Psychological Mood Profile and self-esteem among breast cancer survivors. The participants were 115 Greek women aged between 18-65 (M = 51.97; SD = 4.36) who had been diagnosed with breast cancer and finished oncology treatment or hormone therapy for stage I-IIa cancer for at least one and a half year ago. The Greek versions of POMS, SDS, SIS and IPAQ questionnaires were given to all participants. SPSS 22 package was used for the statistic analysis.

Results: The results indicated that inactive women experienced higher levels of tension (t = 2.05, p < 0.01), higher levels of depression (t = 2.51, p < 0.01) and less self-esteem (t = 2.11, p < 0.01) than active women which were statistically significant. Additionally, they experienced more heightened feelings of anger (t = 1.11, p < 0.01), fatigue (t = 1.58, p < 0.01), confusion (t = 1.08, p < 0.01), start-anxiety (t = 1.46, p < 0.01) and lower vigour (t = 1.12, p < 0.03).

Conclusions: Based on the results it can be concluded that women who exercised before and after treatment on psychological outcomes, mood profile and self-esteem among breast cancer survivors.

Legal entity responsible for the study: Panteion University of Social and Political Sciences of Greece

Funding: Panteion University of Social and Political Sciences

Disclosure: All authors have declared no conflicts of interest.

**Contrast-enhanced ultrasound features of triple-negative breast cancer**

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Background: It is important for triple-negative breast cancer (TNBC) to be detected early for its potential to be aggressive. The purpose of this study was to evaluate the ultrasound and contrast-enhanced ultrasound features of TNBC and to explore symptoms for the diagnosis of TNBC.

Methods: The study retrospectively reviewed 290 patients with postoperative pathology results in our hospital, including 45 cases of TNBC and 255 cases of non-triple-negative breast cancer (NTNBC). All the patients were treated with NAC between January 2011 and July 2015. All of the patients received at least four cycles of chemotherapy, and CUUS images were available before and after the NAC. Using the CUUS program, both quantitative TIC analysis and TA were performed on the CUUS images before and after the NAC. The pathologic breast tumour responses were assessed using the Miller and Payne grade system. Grades 1–3 were categorized as the non-response group, and grades 4–5 were categorized as the response group. The performances of the two quantitative analyses were compared between the non-response and response groups.

Results: For these 21 patients, the TIC analysis identified two parameters, i.e., BI-BIr (p = 0.025) and AUT-AUTr (p = 0.011), that exhibited significant differences between the two groups that are strongly associated with outcomes after NAC, so it could be an independent prognostic factor.

Conclusions: This study demonstrated that quantitative analysis of the features computed from breast CUUS images is a promising tool for evaluating the responses of breast cancers to NAC.

Legal entity responsible for the study: Man Chen, MD & PhD Department of Ultrasound, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University

Funding: National Natural Science Foundation of China (grant number 81772078, 81702378)

Disclosure: All authors have declared no conflicts of interest.

**The effectiveness of neoadjuvant chemotherapy with recombinant tumor necrosis factor-thymosin-1 in locally advanced breast cancer and effect on tumor angiogenesis**

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Background: The little is known about the influence of recombinant hybrid protein of tumor necrosis factor-alpha-thymosin-alpha1 (TNF-T) on angiogenesis in breast cancer (BC). The aim of the study was to investigate markers of angiogenesis and vascular proliferation in the tumor and to evaluate the efficacy of TNF-T in the neoadjuvant treatment of locally advanced breast cancer (LABC).

Methods: Eligibility criteria included LABC of IBII-IIIB stages, ECOG ≤ 2, adequate kidney, liver and bone marrow function, no brain metastasis, TNF-T 200000 IU was used peritumorally (injected around the tumor) on D1-5 (30 min before cytostatics injection), combined with standard FAC or PA regimens. The factors of angiogenesis CD31 and CD34 were studied in trephine biopsy specimens before treatment and in post-surgical biopsies of the tumor after TNF-T courses.

Results: 82 women were recruited between April 2012 - October 2013 (mean age 53 ± 1.1 years). Group A (30 pts) received TNF-T combined to PA (17) and FAC (13) up to 6 courses. Group B (52pts) received standard FAC. Time-intensity curve analysis (TIC) and the MATLAB programme for quantification. The texture analysis revealed that four parameters (Contrast, Entropy, Energy and Homogeneity) exhibited significant differences (< 0.05), and the tumours tended to be more heterogeneous after treatment. Moreover, after NAC, there were 14 cases of non-responders and 7 cases of responders. The areas under the receiver operating characteristic curves of the above parameters, i.e., Contrast, Entropy, Energy, Homogeneity, BI-BIr and AUT-AUTr were 0.799, 0.699, 0.684, 0.770, 0.577 and 0.561, respectively, for the differentiation of the responders from the non-responders.

Conclusions: This study demonstrated that quantitative analysis of the features computed from breast CUUS images is a promising tool for evaluating the responses of breast cancers to NAC.

Legal entity responsible for the study: The effectiveness of neoadjuvant chemotherapy with recombinant tumor necrosis factor-thymosin-1 in locally advanced breast cancer and effect on tumor angiogenesis

**Contrast-enhanced ultrasound for evaluating the response of breast cancer to neoadjuvant chemotherapy: Time-intensity curve analysis and texture analysis**

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Background: The purpose of this study was to investigate the features and performance of contrast-enhanced ultrasound (CEUS) in evaluating the response of breast cancer to neoadjuvant chemotherapy (NAC) using time-intensity curve (TIC) analysis and texture analysis (TA) and the MATLAB programme for quantification.

Methods: The study included 21 breast cancer patients who were treated with NAC between January 2011 and July 2015. All of the patients received at least four cycles of chemotherapy, and CUUS images were available both before and after the NAC. Using the CUUS program, both quantitative TIC analysis and TA were performed on the CUUS images before and after the NAC. The pathologic breast tumour responses were assessed using the Miller and Payne grade system. Grades 1–3 were categorized as the non-response group, and grades 4–5 were categorized as the response group. The performances of the two quantitative analyses were compared between the non-response and response groups.

Results: For these 21 patients, the TIC analysis identified two parameters, i.e., BI-BIr (p = 0.025) and AUT-AUTr (p = 0.011), that exhibited significant differences between the two groups, which indicated that the intensity decreased after treatment. Furthermore, first recurrences in mastectomy patients were often distant metastases, leading to poor prognosis.

Conclusions: I declare that the study presented in the abstract which I am submitting has received funding from the national clinical key specialty construction projects of China.

Disclosure: All authors have declared no conflicts of interest.
complications connected with TNF-T use were observed. By the time of abstract submission OS in Group A was 35.6 ± 1.2mos, in Group B was 34.1 ± 1.1mos, EFS in Group A was 33.3 ± 1.1mos, in Group B was 28.7 ± 1.2mos (p < 0.05). Three-year EFS in group A is 20% higher than in group B (83% and 63% respectively, log-rank test p = 0.04778).

Conclusions: TNF-T injected peri-tumorally allows to increase the antitumor activity of cytostatics (CR) which is of great importance for survival in LABC. The data acquired in the biopsies show that the recombinant protein of TNF-T has the suppressive effect on angiogenesis.

Legal entity responsible for the study: Rostov Institute of Oncology

Funding: Rostov Institute of Oncology

Disclosure: All authors have declared no conflicts of interest.

A phase 2 randomized, double-blind, placebo-controlled trial of radium-223 dichloride with exemestane and everolimus in patients with HER2-negative hormone receptor-positive breast cancer and bone metastases

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Background: Treatment options for bone-dominant metastatic breast cancer (MBC) are limited. Radium-223 (Ra-223) is a beta-emitting targeted radionuclide (Ra) emitter with a targeted antitumor effect on bone metastases (mets), was well tolerated and reduced bone biomarker levels in a phase 2 study in patients with bone-dominant MBC (Coleman et al. Breast Cancer Res Treat 2014). In patients with HER2− hormone receptor− (ER−) bone-dominant MBC, everolimus + exemestane (EVE + EXE) improved progression-free survival (PFS) versus EXE alone. Ra-223 plus EVE + EXE may improve outcomes in patients with HER2− ER− bone-dominant MBC; this trial will evaluate efficacy and safety of Ra-223 versus placebo in these patients (NCT02258451).

Trial design: Eligible patients are pre- or postmenopausal with HER2− ER− MBC and ≥ 2 bone or soft tissue mets. Patients must have measurable disease per RECIST v1.1, ≥ 1 prior line of hormone therapy for MBC, and 1-2 prior skeletal-related events; be on bisphosphonates or denosumab, and have an ECOG score of 0-1. Patients must have had no past or current need for chemotherapy for MBC, no unresolved spinal cord compression, and no prior EVE treatment. Patients are randomized to receive (1:1) Ra-223 (50 kBq/kg [55 kBq/kg after National Institute of Standards and Technology update] IV) or placebo × 6 cycles q 4 wk plus EXE (25 mg PO q.d) + EVE (10 mg PO q.d) plus best supportive care. EXE + EVE continues until disease progression or unacceptable toxicity. Stratification is by geographic region (EU/N Amer vs Asia), prior hormone therapy (1 vs 2), and presence of visceral disease (yes vs no). Safety and efficacy are assessed every 4 weeks. Long-term safety is assessed until study termination. The primary end point is symptomatic skeletal event–free survival (SSE-FS). Secondary end points are overall survival; times to opiate use, pain progression, and chemotherapy; radiologic PFS; and safety. Assuming a 1-sided α = 0.025 with 80% power, 480 patients are required for the analysis. Safety analysis will be descriptive. Estimated enrollment is ~ 311 patients. Currently, 72 patients are randomized.

Clinical trial identification: NCT02258451

Legal entity responsible for the study: Pharmaceuticals Division of Bayer

Funding: Pharmaceuticals Division of Bayer

Disclosure: H. Rugo: Speakers bureau, honoraria: Genomic Health; research funding: Plexxikon, Macrogenics, OBI, Eisai, Pfizer, Novartis, Lilly, GlassoSmithKline, Genentech, Celstion, Nektar, Merk; travel, accommodations, expenses: Novartis, Nektar, Roche/Genentech, OBI, Mylan. O. Petreniciuc: Employed by and travel, accommodations, expenses from Bayer. A. Zhang, R. Li: Employed by Bayer. R.E. Coleman: Expert testimony for Novartis; research funding from Bayer.
abstracts

211TP A phase III study of alpelisib and fulvestrant in men and postmenopausal women with hormone receptor-positive (HR+) human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (BC) progressing on or after aromatase inhibitor (AI) therapy (SOLAR-1)
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Background: The phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway is often dysregulated in HR+ BC and is associated with resistance to endocrine therapy (ET). Alpelisib (BYL719, PI3Kα/δ-specific inhibitor) and fulvestrant (FV; selective estrogen receptor-downregulator) are second-line agents approved for HR+ BC progressing on prior ET. The study evaluated the efficacy and safety of alpelisib plus fulvestrant versus placebo plus fulvestrant for men and postmenopausal women with HR+ HER2- advanced BC. Aims: To evaluate the primary endpoint: PFS, and to assess the secondary endpoints: OS, PFS in the PIK3CA non-mutant cohort, EFS and safety. Results: A total of 503 patients were randomized to alpelisib plus fulvestrant (N=251) or placebo plus fulvestrant (N=252). The PFS was 16.2 months (95%CI: 14.0-18.0) in the alpelisib group and 6.9 months (95%CI: 5.9-8.7) in the placebo group (HR=0.38, 95%CI: 0.28-0.52; median follow-up: 16.6 months). The PFS in the PIK3CA non-mutant cohort was 15.0 months (95%CI: 12.6-17.7) and 5.8 months (95%CI: 4.4-7.9) for the alpelisib and placebo groups, respectively (HR=0.31, 95%CI: 0.19-0.51). A total of 403 patients (80%) were evaluable for efficacy and 497 (99%) patients were evaluable for safety. In the alpelisib group, the most observed grade ≥3 adverse events were hyperglycemia (17.5%), diarrhea (13.5%), fatigue (12.7%), and nausea (12.7%). There were 10 deaths (4.0%) in the alpelisib group and 11 deaths (4.4%) in the placebo group. Conclusion: Alpelisib plus fulvestrant significantly improved PFS compared with placebo plus fulvestrant. The median PFS in the PIK3CA non-mutant cohort was also significantly improved in the alpelisib group. The most observed grade ≥3 adverse events were hyperglycemia, diarrhea, fatigue, and nausea. The conclusion of this study on the basis of the results presented does not adhere to all clinical regulatory standards of Novartis. S. Lobin: My institution has received research funding from the majority of pharmaceutical companies i.e. but not limited to Novartis, Pfizer, Amgen, Roche, AZ, Celgene. H. Tesch: Consulting activities: Novartis, Roche, Pfizer Fees: Novartis, Roche, Pfizer, A.S. Longin: Employment, leadership. Research funding and travel/accommodation/expenses: Novartis. D. Mills: I own stock in Novartis Pharma AG. C. Wilke: Employee of Novartis AG, sponsor of the study. C. Germa: Employment and stock ownership: Novartis. M. Campone: Novartis advisory board speaker bureau Menarini: advisory board speaker AstraZeneca: advisory board speaker Pfizer: advisory board speaker bureau Roche: Advisory board. All other authors have declared no conflicts of interest.

212TP A phase 2 randomized, double-blinded, controlled study of ONT-380 vs. placebo in combination with capecitabine (C) and trastuzumab (T) in patients with pretreated HER2+ unresectable locally advanced or metastatic breast carcinoma (MBC)
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Background: 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, ONT-380 demonstrated synergistic activity with T, and was active in HER2+ models of brain metastases (mets). In a Phase Ib study, ONT-380 was combined with C and T in pts with HER2+ MBC previously treated with trastuzumab emtansine (T-DM1) and T. Objective response rate (ORR) was 13/24 (54%) in pts with measurable disease treated with ONT-380 + C + T (including 10 pts with brain mets). The combination was well tolerated, with low rates of GI diarrhea at the recommended dose (300 mg PO BID, equivalent to the single agent MTD). Based on these data, ONT-380 is now being evaluated in a Phase 2 study in combination with C and T.

Trial design: The primary study objective is to assess the effect of ONT-380 vs placebo given with C + T on progression-free survival (PFS) based on independent central review. Additional secondary objectives include CNS PFS, non-CNS PFS, non-CNS mets progression, ORR, duration of response, clinical benefit rate, and safety. The study population includes adult pts with progressive HER2+ locally advanced or MBC who have had prior treatment with a taxane, T, pertuzumab and T-DM1 but not or lapatinib. Pts with brain mets, including untreated or progressive mets, may be enrolled. 180 pts will be enrolled in North America and Europe. Pts will receive C (1000 mg/m² PO BID for 14 days of a 21-day cycle) and T (9 mg/kg IV loading dose, 6 mg/kg IV once every 21 days), and will be randomized in a 2:1 ratio to receive ONT-380 300 mg PO BID or placebo. Pts with isolated CNS mets progression may continue on study treatment after undergoing local CNS therapy. An independent Data Monitoring Committee will monitor pt safety.

Clinical trial identification: ONT-380-206
Legal entity responsible for the study: Oncothyreon Inc.
Funding: Oncothyreon Inc.
Disclosure: G. Curigliano: ESMO Faculty and ESMO Multi-Committee member. Please refer to the declaration uploaded previously. All other authors have declared no conflicts of interest.

213TP SANDPIPER: Phase III study of the PI3-kinase (PI3K) inhibitor taselisib (GDC-0032) plus fulvestrant in patients (pts) with oestrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer (BC) enricd for pts with PIK3CA-mutant tumours
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Background: The PI3K signalling pathway is one of the most dysregulated in BC. The alpha (α) isoform of the catalytic subunit of PI3K, encoded by PIK3CA, is mutated in ~40% of ER-positive, HER2-negative breast tumours. Mutations in PIK3CA promote tumour growth and proliferation and can mediate resistance to endocrine therapies. The potent and selective PI3K inhibitor, taselisib, displays greater selectivity for mutant PIK3CA compared with wild-type PI3Kα, and has demonstrated enhanced activity in PIK3CA-mutant BC cell lines. In pts with PIK3CA-mutant BC, confirmed partial responses were reported following treatment with either single-agent taselisib or taselisib in combination with fulvestrant.

Legal entity responsible for the study: Oncothyreon Inc.
Funding: Oncothyreon Inc.
Disclosure: G. Curigliano: ESMO Faculty and ESMO Multi-Committee member. Please refer to the declaration uploaded previously. All other authors have declared no conflicts of interest.

Clinical trial identification: SOLAR-1-NCT02413711

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Annals of Oncology

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HERMIONE: A phase 2, randomized, open label trial comparing MM-302 plus trastuzumab to chemotherapy of physician’s choice plus trastuzumab, in anthracycline naïve HER2-positive, locally advanced/metastatic breast cancer patients previously treated with pertuzumab and T-DM1

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Background: Although HER2-targeted therapies such as pertuzumab and ado-trastuzumab emtansine (T-DM1) have improved patient outcomes, treatment resistance typically occurs. MM-302 is a HER2-targeted antibody-liposomal doxorubicin conjugate in development by Merrimack Pharmaceuticals. In a Phase 1 study, patients with HER2-positive metastatic breast cancer (MBC) were treated with MM-302 alone and in combination with trastuzumab with or without cyclophosphamide. MM-302 had an acceptable safety profile, and promising efficacy was observed in patients not previously exposed to an anthracycline.

Trial design: HERMIONE is a randomized Phase 2, two-arm, open-label trial in patients with anthracycline naïve, trastuzumab-, pertuzumab- and T-DM1-treated HER2-positive locally advanced breast cancer (LABC)/MBC. Patients are randomized 1:1 to receive MM-302 (10mg/m², Q3W) plus trastuzumab (6mg/kg, Q3W) or chemotherapy of physician’s choice (vinorelbine, capecitabine, or gemcitabine) plus trastuzumab (6mg/kg, Q3W).

Eligibility criteria: Centrally confirmed HER2-positive/LABC/MBC, no prior anthracycline exposure, prior trastuzumab, prior T-DM1 in the LABC/MBC setting, prior pertuzumab in the LABC/MBC setting, disease recurrence within 12 months of neoadjuvant/adjuvant treatment, unlimited prior lines, ECOG 0-1 and LVEF ≥50%. CNS metastases are permitted if stable and without symptoms or steroids for 4 weeks.

Specific aims: The primary endpoint is progression free survival (PFS) assessed by an independent blinded review. Secondary endpoints include investigator assessed PFS, overall survival, response rate, safety and patient related outcomes.

Statistics: 250 patients will be enrolled to observe 191 PFS events for 90% power to detect a HR of 0.625. The MM-302 arm will be compared to the control arm on the primary endpoint of PFS using a stratified log-rank test at one-sided 0.025 level.

Status: First patient treated was in December 2014 and enrollment is expected to be complete in 2017. Sites are open in the US, Canada and Western Europe.

Clinical trial identification: NCT02213744

Legal entity responsible for the study: Merrimack Pharmaceuticals

Funding: Merrimack Pharmaceuticals


Treatment assessment: Clinical investigators will assess response, progression, and safety according to Response Evaluation Criteria in Solid Tumors (RECIST). Other endpoints include overall survival, response rate, tolerability, health outcomes, and pharmacokinetics. Assuming a hazard ratio of 0.625, the study yields 80% statistical power to detect superiority of Arms A and B over Arm C tested sequentially at a 1-sided alpha level of 0.10 (NCT02675231).

Clinical trial identification: EudraCT Number: 2015-003480-24, start date 29 January, 2016

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company

Background: Accurate and unbiased assessment of tumor response or progression is crucial in randomized control trials. Blind independent central reviews are usually used as a supplement or monitor to local investigator assessment but are costly. It is worth determining the value of central assessment.

Methods: We compared central and local assessments by study-level pooling analysis and correlation analysis, primarily through investigating treatment effects of objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and tumor-shrinking progression (TTP). Evaluation for response between two assessments was also compared. Eligible trials were phase III RCTs of anti-cancer drugs for non-hematologic solid tumors, searched in PubMed between the dates of Jan 1, 2010 to Jun 24, 2015.

Results: Of 61 included trials involving 37,396 patients, 10 (16%) trials were with different statistical conclusion regarding primary or secondary endpoints between two assessments. However, pooling analysis found no significant difference when comparing estimating treatment effects between two assessments, pooled odds ratios (OR) of ORR, DCR, PFS and TTP were 1.03 [0.95–1.09], 0.96 [0.90–1.03], 1.01 [0.99–1.03] and 1.04 [0.95–1.14], respectively. This concordant outcome could be found regardless of mask (open/blind), region (global/intercontinental), tumor type, study design (superiority/non-inferiority), criteria of tumor assessment (RECIST/WHO). Correlation analysis also indicated their concordance on treatment effects (ORR, DCR, PFS: r = 0.80, p < 0.01; TTP: r = 0.896, p = 0.293). Synthesis for response evaluation indicated central ORR and DCR were numerically higher than those of the local in both experimental arms and control arms, without evaluation bias (ORR: OR = 1.02 [0.97–1.08]; DCR: OR = 0.96 [0.90–1.03]).

Conclusions: Central assessment remains an irreplaceable method but the necessity to apply it in a complete-case fashion should be questioned regarding efficiency, especially in trials with double-blind design. A modified strategy, such as sampling central assessment, warrants further evaluation.

Legal entity responsible for the study: N/A

Funding: The First Affiliated Hospital of Guangzhou Medical University

Disclosure: All authors have declared no conflicts of interest.

Valuing the effect sizes hypothesized in phase 3 trials published from 2005 to 2015

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Background: We sought to determine the effect sizes hypothesized (ESH) for phase 3 trials of targeted therapies, and to compare them against frameworks for assessing the magnitude of benefit from anti-cancer treatments recently proposed by ESMO (Cherny et al Ann Onc 2015), and ASCO (Schipper et al JCO 2015), and against recommendations for designing phase 3 trials (Ellis et al JCO 2014).

Methods: We searched Medline from 2005-15 for phase 3 trials of targeted therapies, including immunotherapies, in metastatic solid organ malignancies, designed with a superiority hypothesis. For each trial’s primary endpoint, we determined the ESH in relative terms (typically a hazard ratio [HR]), and in absolute terms (typically a difference in median survival times or rates). The hypothesised effect size was assigned a clinical benefit score according to the ESMO and the ASCO frameworks for valuing benefit. Sufficient information was available to determine both the relative and absolute ESH in 141 of the 203 included trials (69%), only the relative ESH in 53 (26%), only the absolute ESH in 0, and neither relative nor absolute ESH in 9 (4%). The 2014 ASCO framework proposed that phase 3 trials should be designed with a HR ≤ 0.94 was met by the majority of trials (90/102, 90%) with a primary outcome of overall survival. The majority of these phase 3 trials had hypothesized effect sizes that were judged to reflect modest clinical benefits by both frameworks: ESMO 169/203 trials, 83% and ASCO 152/203 trials, 75% (see table).

Table: 317P

<table>
<thead>
<tr>
<th>ESH magnitude of clinical benefit</th>
<th>Primary outcome of ORR N = 102 (%)</th>
<th>Primary outcome of PFS or TTP N = 94 (46%)</th>
<th>Total number of trials that meet criteria N = 203 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least benefit</td>
<td>9 (9%)</td>
<td>79 (39%)</td>
<td>88 (43%)</td>
</tr>
<tr>
<td>ASCO criteria for clinical benefit (%) improvement in outcome</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>1.00 (9%)</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>3</td>
<td>1.05 (9%)</td>
<td>13 (6%)</td>
<td>14 (7%)</td>
</tr>
<tr>
<td>4</td>
<td>1.10 (9%)</td>
<td>7 (3%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Most benefit</td>
<td>1.20 (9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Conclusions: Only 69% of these phase 3 trials included sufficient information to determine both the relative and absolute effect sizes hypothesized. The majority of trials were powered to show magnitudes of clinical benefit rated modest by the ESMO and ASCO frameworks. Trial protocols and reports should specify both the relative and absolute benefits hypothesized.

Legal entity responsible for the study: The University of Sydney

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Disclosure: All authors have declared no conflicts of interest.

Comparison of the EORTC criteria and PERCIST in solid tumors

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Background: There are two sets of criteria using PET to monitor metabolic changes to anti-cancer treatment: the criteria developed by the European Organization for Research and Treatment of Cancer (EORTC criteria) and the PET Response Criteria in Solid Tumors (PERCIST). We conducted this pooled study to investigate the strength of agreement between the EORTC criteria and PERCIST in the assessment of tumor response.

Methods: We searched for all relevant studies written in English through the following search strategy: A systematic literature search of MEDLINE, PUBMED, and EMBASE from 2009 when the PERCIST criteria were proposed to January 2016 was carried out to find articles including the following terms in their title, abstract, or key words: ‘tumor response’, ‘EORTC criteria’, or ‘PERCIST’. We used the related articles feature of the PUBMED to identify the related articles. Articles were considered for inclusion in this pooled study if they compared tumor responses by the EORTC criteria and PERCIST.

Results: There were six articles with the data on the comparison of the EORTC criteria and PERCIST. A total of 348 patients were collected; 190 (54.6%) with breast cancer, 45 with colorectal cancer, 45 with lung cancer, 14 with basal cell carcinoma in the skin, 12 with colorectal cancer, and 6 with head and neck cancer. The agreement of tumor response between the EORTC criteria and PERCIST was excellent (k = 0.946). Of 348 patients, only 12 (3.4%) showed disagreement between two criteria in the assessment of tumor response. The shift of tumor response between two criteria occurred mostly in patients with PMR and SMD. The estimated overall response rates were not significantly different between two criteria (72.7% by EORTC vs. 73.6% by PERCIST).

Conclusions: In conclusion, this pooled study demonstrates that the EORTC criteria and PERCIST showed almost perfect concordance in the assessment of tumor response in patients with solid tumors. However, it is still necessary to investigate the differences between the criteria in studies with larger homogeneous patients’ cohort to elucidate if the criteria can be used interchangeably in clinical practice.
Systematic review of adverse events reporting in clinical trials leading to approval of targeted therapy and immunotherapy

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Background: Reporting toxicities of targeted therapies (TTs) and immunotherapy in oncology requires care in respect to way of measurement, duration of adverse events (AEs) and impact on treatment dose intensity. New drugs are approved by regulatory agencies on the basis of the safety and efficacy results deriving from pivotal trials, but the impact on broader use is often misunderstood.

Methods: We identified the TTs and immunotherapies approved by FDA for solid malignancies in adult patients from 2000 to October 2015. The trials which led to this indication were retrieved from the FDA website. Publications were reviewed according to a 24-point score based on the Consolidated Standards of Reporting Trials (CONSORT) guidance.

Results: We identified 81 trials, mainly performed in colorectal, lung, breast cancer and melanoma, globally involving more than 45,000 patients. The experimental drug was studied as single agent in 51% of the cases and associated with chemotherapy in 32%; setting of trials was mainly the treatment of advanced disease (95% of the trials). When specified, the median rate of elderly population (> 65 years) who were treated was 37%. The items that reported the higher proportion of trials with a low score in AEs description are the following: reporting frequent and late toxicities and duration of the AEs (in more than 80% of the trials), description of time of occurrence (86% of the trials) and indication of all AEs, instead of only those occurred with a frequency above in more than 90% of the trials); description of non-primary endpoints.

Conclusions: The clinical trial registry is intended to serve as a transparent public database of clinical trials. However, according to our research, the majority of RCTs in high-impact journals demonstrate registry/protocol discrepancies in the listing of non-primary endpoints.

Legal entity responsible for the study: Victoria Serpas

Funding: MD Anderson Cancer Center

Disclosure: All authors have declared no conflicts of interest.

320P Re-treatments after gamma knife radiosurgery for metastatic brain disease

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Background: Gamma Knife radiosurgery (GKR) has become a first line treatment option for brain metastases resulting in high local tumor control. As systemic therapies improve and survival prolongs, local recurrences and new brain metastases are more likely to occur following GKR, with may increase the need for secondary treatments. In this report we evaluated the number of patients receiving re-treatments, the timing and kind of re-treatments, as well as the survival after treatment of local recurrences and new brain metastases in a group of patients initially treated with GKR alone.

Methods: We performed a retrospective analysis of 806 patients with histologically confirmed metastatic cancer, of all primary origins, who underwent GKR in our center between January 2009 and December 2014. All the brain metastases that were visible description of the toxicities leading to therapy withdrawal and in follow up interval assessment were present in more than 50% of the analysed papers. Dose reductions due to AEs were not reported in 1 out of 3 trials.

Conclusions: Suboptimal reporting of AEs in trials leading to approval of TTs and immunotherapy was shown. Improving AEs' caption and description should be a priority in ongoing trials as well as post-marketing safety analysis. This is particularly true for AEs of new drugs, frequently mild or moderate in severity but potentially longer in duration and recurrent, with a clear impact on patients' quality of life.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

321P The new European Clinical Trial Regulation: Perception, expectations and experiences in Italy

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Background: In the last decade Europe has faced a sharp slowdown in Clinical Research (CR) mainly due to European Directive 2001/20/CE application. Consequently the European Commission enacted the EU Regulation 536/2014 (ER) that is expected to become effective only in 2018, due to delays in the portal development. To investigate the ER perception and knowledge of the Italian professionals, two online surveys, addressed to Clinical Research Coordinators (CRCs) and Clinical Investigators (CIs), were conducted.

Methods: Two anonymous web-based surveys, both consisting of 17 questions, have been used.

Results: The 62.5% and 38.9% of the contacted CIs and CRCs respectively answered to the survey: 12% of the CIs have a full knowledge of the incoming ER while many are only partially (64%) or not (24%) informed. 80.4% of CRGs demonstrate a complete knowledge and are already trained. Amongst the evaluated topics, the need of a Reporting Member State in the first stage of the evaluation process is considered as positive by 74% of the CIs and almost (90%) believe that this procedure will reduce the approval time. With regards to newly imposed transparency standards, 86% of the CIs would welcome the publication of trial results, while 14% believe that this obligation should only apply to profit trials. Overall 70% of CIs state that staff site’s facilities already met all of the ER imposed qualification. The 50% of CIs foresee that the ER will promote independent CR while 42% suppose that it will essentially affect the profit trials. Even though 71.4% of CRGs do not have a definite opinion on ER, 85.7% is convinced that it will have a direct impact on their job.

Conclusions: The ER is a turning point for European CR: it is designed to ensure faster procedures, with positive effects both on timing and overall costs and it will require a rigorous methodology and an increased quality. The surveys highlighted different opinions among CIs and CRGs on Italian ability to rise to this challenge: while CIs believe that the centers already met the imposed requirements with only an initial period of transition, CRGs are less optimistic. This process will involve big efforts and resources, but the payback is the opportunity to be on board of innovative treatments for the Italian patients.

Legal entity responsible for the study: Institute for Cancer Research and Treatment, Candolo (TO) - Italy

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Disclosure: All authors have declared no conflicts of interest.

319P Selective registration of non-primary endpoints in randomized clinical trials in oncology: a comparison of endpoint reporting between clinical trial protocols and US national clinical trial registration

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Background: Randomized clinical trials represent the cornerstone of evidence-based medicine. Despite the implementation of clinical trial registration, the completeness of such reporting has not been well studied.

Methods: We analyzed oncology-based randomized clinical trials (RCTs) conducted in 2012 in the Journal of Clinical Oncology, New England Journal of Medicine, and The Lancet. The primary endpoints and non-primary endpoints from each clinical trial protocol (a required supplement for publication in these journals) and the corresponding listing on the US national clinical trial registry (clinicaltrials.gov) were collected. Secondary, exploratory, correlational, end points were considered non-primary end points. Registry/report discrepancies were then quantitatively and qualitatively evaluated.

Results: Out of the 58 RCTs, primary endpoint registry/report discrepancies occurred in only 2 trials (3%). However, registry/report discrepancies in non-primary endpoints occurred in 46 trials (79%). Of these 46 trials, 39 (85%) had non-primary endpoints found in the protocol but not in the registry. Of these 39 trials, 10 discrepancies related to exploratory or translational endpoints mentioned in the registry, and 6 related to the endpoint of safety missing from the registry. Of the 46 trials with non-primary endpoint registry/report discrepancies, 20 (43%) had non-primary endpoints found in the registry that were not found in the protocol. 18 of these 20 trials had de novo endpoints not listed anywhere in the protocol and 2 had endpoints listed in the protocol but not within the respective objective/endpoint section. Registry/report discrepancies regarding time-to-event endpoints occurred in 12 trials (21%), with 10 related to omission of such endpoints from the registry.

Conclusions: The clinical trial registry is intended to serve as a transparent public database of clinical trials. However, according to our research, the majority of RCTs in high-impact journals demonstrate registry/protocol discrepancies in the listing of non-primary endpoints.

Legal entity responsible for the study: Victoria Serpas

Funding: MD Anderson Cancer Center

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Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

All authors have declared no conflicts of interest.
on the high resolution triple dosed gadolinium planning MR imaging (n = 2180) were treated. In all cases, a dose of 18-25 Gy was prescribed to the isodose covering 99-100% of the tumor volume. All patients had a Karnofski index ≥70 and had no prior treatment to the brain.

Results: A median survival of 6 months (95%CI: 5.3-6.7) was found in the studied population (n = 806; 51% male; mean age 63 years). Per patient a median of two brain metastases were treated at first GKR (Range 1-15). Retreatment was given to 289 patients (36%) out of whom 69% received GKR as the second treatment, 14% received whole brain radiotherapy (WBRT), 12% underwent resection and 5% received other re-treatments. Patients receiving re-treatment had a median survival of 13 months (95%CI: 11.3-14.7) versus patients not receiving re-treatment with a median survival of 4 months (95%CI: 3.6-4.4). The median interval between the first GKR and the second treatment was 6 months. Out of the deceased patients most died within the first 3 months (35%). Most patients died due to their extracranial disease (61-66%).

Conclusions: About one third of patients treated with GKR for brain metastases in our center received a secondary treatment to the brain along the course of their disease. Repeat GKR was given to the majority of these patients. Re-treatment of new brain metastases or local recurrence appeared to be an effective therapy as most patients died due to extracranial disease.

Legal entity responsible for the study: Dr. Hannens, Gamma Knife Center Tilburg

Funding: Gamma knife center Tilburg

Disclosure: All authors have declared no conflicts of interest.
Background: Molecular characterization of low grade gliomas (LGG) has improved in recent years and is essential for diagnosis and treatment of these diseases. Moreover, clinical factors, such as age and the extent of surgery retain a prognostic role in LGG that were assessed for IDH1/2, 1p/19q codeletion, and MGMT methylation status.

Methods: We retrospectively evaluated all adult LGG patients (pts) from our database who received surgery and had sufficient tissue to assess biomarkers characterization. IDH1/2 assessment was performed on formalin-fixed paraffin-embedded samples by PCR, MGMT by methylation specific PCR, 1p/19q codeletion by FISH.

Results: 198 consecutive LGG were included. The median age was 38 (range: 18–72). Median follow up was 74.0 months, 109 pts (55.1%) were <40 years of age, 26 pts (13.1%) underwent biopsy, 119 pts (60.1%) partial resection, 53 pts (26.8%) complete resection. Twenty-eight pts (14.2%) were considered low risk (<40 years with complete resection). IDH1/2 mutation was found in 79.8% of pts. 1p/19q codeletion was found in 41.4% of pts, MGMT methylation in 57.1% of pts. Median survival in low risk resection was 211.0 months (95%CI: 190.4–231.6) and was 145.3 months (95%CI: 103.3–182.2) in high risk patients (P = 0.006). Median survival for patients with IDH1/2 mutation was 159 months (95%CI: 103.3–214.7) and was 87 months in patients IDH1/2 wild type (95%CI: 61.1–114.6, P < 0.001). Multivariate analysis showed that clinical risk (P = 0.004), IDH1/2 mutation (P = 0.001) and 1p/19q codeletion (P = 0.03) were significantly correlated with overall survival. MGMT methylation was not significant.

Conclusions: Molecular characteristic of LGG define the prognosis of these tumors. Moreover, clinical risk assessment retain a role even in the era of molecular characterization.

Legal entity responsible for the study: Azienda USL / IRCCS Institute of Neurological Sciences of Bologna

Funding: Azienda USL / IRCCS Institute of Neurological Sciences of Bologna

Disclosure: All authors have declared no conflicts of interest.
Clinical trial identification: NCT01351870

Legal entity responsible for the study: AbbVie, Inc.

Funding: AbbVie, Inc.

Disclosure: A.B. Lassman: Comp/Res Support: VBI Vaccines, SanofiTherapeutics, Omniox, Celldex; is involved in speakers bureaus with Roche and Merck; received research funding from AbbVie and Roche. K.P. Papadopoulos: Received research funding from AbbVie, Pfizer and Merck Serono; affiliated with the Ludwig Institute for Cancer Research. N. Butowski: Received honoraria from and stock. R. Merrell: Advisory Board for AbbVie. All other authors have declared no conflicts of interest.

PD-1 and IL-17 expression in tumor infiltrating lymphocytes are opposite prognostic factors in glioblastoma

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Background: Glioblastoma (GB) is the most frequent malignant primary brain tumor. Median overall survival (OS) is only 15 months despite recent progress with the association of temozolomide and radiotherapy. Tumor infiltrating lymphocytes (TIL) are present in GB stroma but their influence on prognosis is not clearly defined. The purpose of this retrospective study was to explore the prognostic value in GB of tumor infiltration by IL-17 (interleukin 17), CD4+ and PD-1+ (programmed death ligand 1) expressing lymphocytes.

Methods: All included patients had surgery followed by radiotherapy and temozolomide (Stupp’s regimen). IL-17, CD4+ and PD-1+ were assessed by immunohistochemistry in a cohort of 77 GBM. Number of positive cells were counted in a X40 field. We used the software cutoff finder to determine the optimal cut off to distinguish between patients with high or low infiltrate. Logrank analysis and Cox proportional hazard models were used to determine overall survival factors in function of type and number of TIL.

Results: In univariate analysis, high number of IL17 expressing cells was correlated with poor OS (HR = 1.7 IC[1.1-1.99] p = 0.03). High PD-1+ infiltration was correlated with a better prognosis 50% of GBMs harbor EGFR amp. ABT-414 monotherapy has shown preliminary efficacy in EGFR amp GBM. Here we report safety and efficacy of ABT-414 + TMZ in EGFR amp GBM at the recommended phase 2 dose.

Background: Adults with rGBM harboring centrally-confirmed EGFR amp, adequate end-organ function, and KPS ≥70 were eligible. To isolate the effects of ABT-414 from other prior therapies, all patients (pts) were TMZ refractory, defined as a recurrent/progressive disease <3 months from last TMZ. Pts received ABT-414 1.25 mg/kg IV on days 1 and 15, and TMZ 150-200 mg/m² on days 1-5 of 28-day cycles, until progression (RANO).

Results: As of March 1, 2016, 32 pts were treated following 1 (n = 21), 2 (n = 8), or >3 (n = 3) prior therapies. The most common adverse events (AEs) (≥23% pts) were blurred vision (53%), photophobia (34%), headache (34%), fatigue (31%) and constipation (25%). Grade 3/4 AEs included (≥1 pt) leukocytosis (16%), ataxia, decreased platelet count, hemorrhage and thrombotic Sophia (6% each). Seizure was the most common serious AE, occurring in 13% pts. Neurologic AEs were generally attributed to the underlying tumor. No dose-limiting toxicities were observed. Best radiographic responses in 31 pts with available imaging data were: 3 (10%) partial responses (PR), 18 (58%) stable disease (SD), and 10 (32%) progressive disease (PD). Pts with PD were allowed a repeat resection as clinically indicated. Four of them were found to have all or mainly treatment effect rather than active recurrence on histologic analysis; the progression-free survival (PFS), response, and 6 month PFS rates will be updated after clarifying their outcomes.

Conclusions: In this TMZ refractory population, ABT-414 demonstrated 10% PR and 58% SD rates, although histology of tissue resected for presumed recurrence remains to be clarified, which may increase rate of disease control. No new safety events were observed and ocular toxicity was the most common AE. A global, randomized trial of ABT-414 alone or with TMZ, or TMZ or lomustine, is underway in GBM (NCT02343406).

Clinical trial identification: NCT01800695

Legal entity responsible for the study: AbbVie, Inc.

Funding: AbbVie, Inc.

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Routine molecular subgrouping of medulloblastoma: Bridging the divide between research and the clinic using low-cost, mass spectrometry-based DNA methylation

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Background: DNA methylation patterns allow the subclassification of medulloblastoma (MB) into 4 molecular subgroups, which inform treatment and risk-stratification. Whilst microarrays to assign subgroup are suitable for research, their clinical utility is limited by expense, platform specificity, sample quantity requirements and practicality. Here, we aimed to develop a low-cost, array-independent, robust subgrouping assay for routine quality-controlled subclassification, including scant, poor-quality, aged samples, and apply it to the previously unassignable PNET4 trial.

Methods: Using a cross-validated classification model, a minimal, multiply-redundant, 17-locus signature was derived to assign subgroup from 220 MBs profiled using Illumina 450k DNA methylation arrays. We next adapted the MALDI-TOF Mass Spectrometry (MassARRAY, Agena Bioscience) iPLEX assay to interrogate DNA methylation following bisulfite treatment. After in vitro validation, the assay was applied to 101 DNA extracts from fresh-frozen, FFPE and nucleic (<90,000 nuclei) tumoral material. Subgroup assignments from an optimised classifier were compared against gold-standard 450k calls. Following validation, subgrouping was attempted for standard-risk PNET4 samples where possible.

Results: 95/101 validation samples had high-confidence assignments which recapitulated 450k subgroup calls. Subsequently, high-confidence calls were made for 107/153 PNET4 samples. Notably, a worse survival was observed for standard-risk PNET4 Grp4 patients (EFS 80%; p = 0.01).

Conclusions: MBs can be routinely subgrouped using minimal DNA methylation signatures. The assay is suitable for reliable, robust testing of poor-quality, degraded samples using <100ng DNA. The assay’s low-cost, rapidity and applicability to single samples demonstrate its potential for routine use. It can be retrospectively applied to archival cohorts where material is scant to contemporise historical studies. This first demonstration of multiplexed, methylation subtyping holds rich promise for future molecular subclassification and prognostication across diverse tumour types using methylation.
Conclusions: This study underline that PDL1 infiltrate and IL-17 are associated with outcome in a cohort of 77 patients with GBM that received an optimal treatment with surgery and radiochemotherapy. Such data support rational to test PD-L1 and IL17 targeted immunotherapy in GBM.

Legal entity responsible for the study: Centre Georges François Leclerc, Dijon, CHU Amiens

Funding: CHU Amiens

Disclosure: All authors have declared no conflicts of interest.

328PD Effectiveness of antiangiogenic drugs (ADs) in glioblastoma (GBM) patients (PTS): a metaanalysis of randomized clinical trials (RCTs)

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Background: CEBs are highly vascularized tumors and various ADs have been investigated in clinical trials showing unclear results. We performed this metaanalysis to evaluate the effectiveness of ADs, in terms of progression-free survival (PFS) and overall survival (OS), as first or second-line therapy and their association with chemotherapy in GBM PTS.

Methods: The authors searched relevant published and unpublished RCTs analyzing ADs versus chemotherapy in GBM PTS from 2000 to January 2016 in MEDLINE, WEB of SCIENCE, ASCO, ESMO and SNO databases.

Results: Sixteen RCTs (9 with bevacizumab, 2 cilengitide, 1 enzastaurin, 1 dasatinib, 1 vandetanib, 1 temsirolimus, 1 cediranib) were identified including 4566 PTS. All trials showed no improvement in OS with a pooled HR of 1.02 (95% CI 0.93-1.11; p = 0.7). No improvement of OS was shown when BEV was associated with chemotherapy (2388 PTS with a pooled HR of 0.99 (95% CI 0.88-1.11; p = 0.8). Seven RCTs with a different AD demonstrating no improvement of OS versus standard treatment with a pooled HR of 1.05 (95% CI 0.89-1.23; p = 0.5). 14 RCTs (4549 PTS) were analyzed for PFS and the use of ADs showed a statistically longer PFS with a pooled HR of 0.73 (95% CI 0.62-0.86; p < 0.01). However, among ADs, only bevacizumab (2725 PTS) demonstrated an improvement of PFS, indeed, the pooled HR for BEV studies was significant at HR = 0.6 (95% CI 0.5-0.7; p < 0.01), both alone (HR = 0.6; CI 0.4-0.8; p < 0.01) or in combination to CT (HR = 0.6; 95% CI 0.4-0.7; p < 0.01), both as first-line treatment (HR = 0.65; 95% CI 0.52-0.83; p < 0.01) or in recurrent disease (HR = 0.51; 95% CI 0.43-0.61; p < 0.001).

Conclusions: ADs did not improve OS in GBM PTS, but as first or second-line treatment. Among ADs, only BEV demonstrated a PFS benefit both as single agent or in combination with chemotherapy, both as first- or second-line treatment.

Legal entity responsible for the study: IOV

Funding: None

Disclosure: All authors have declared no conflicts of interest.

329PD Survival of patients with synchronous and metachronous breast cancer and meningioma

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Background: The prognostic relevance of the association between Breast Cancer (BC) and Meningioma (M) is still unknown. Therefore, our aim was to evaluate the survival impact of tumor exposure sequence - synchronous or metachronous - in patients with these tumors.

Methods: Patients were divided in three groups according to the exposure variable: these tumors.

Results: A total of 1715 patients were followed for a median follow-up of 84 months.

Conclusions: The BC + M group had the shortest survival (median of 32 months) and BC → M the longest (median of 110 months). The unadjusted analysis revealed BC → M group as statistically related to the shortest survival (HR 3.13, 95%CI [1.62-6.04]). The adjusted analysis confirmed that the BC → M group was the one with worst prognosis (HR 3.11, 95%CI [1.58-6.19]), with no statistical difference between the metachronous tumors. Increasing age (HR 1.13, 95%CI 1.11-1.15, p < 0.005) and grade III meningioma (HR 4.51, 95%CI 1.90-10.69, p = 0.005) were related with lower survival. Meningioma treatment has no influence in survival (p = 0.05) and breast cancer... Grade III meningioma and receptor hormonal status influenced synchronous tumors (p < 0.05) but have no influence on metachronous tumors survival (p < 0.05) on stratified analysis.

Legal entity responsible for the study: Clinical Scholars Research Training Program, Harvard Medical School Portugal

Funding: None

Disclosure: All authors have declared no conflicts of interest.

330PD Temporal muscle thickness (TMT) is an independent prognostic parameter in patients with newly diagnosed brain metastases (BMI) of breast cancer (BC)

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Background: Sarcompenia has been described as objectively measurable parameter indicating frailty and adverse prognosis in several cancer types. We thus hypothesized that TMT may serve as surrogate marker of frailty.

Methods: 189 BC patients (luminal A: 45/189 (23.8%), HER2: 75/189 (39.7%), triple negative: 35/189 (18.5%), unknown subtypes: 34/189 (18.0%), all female with a median age of 54 years (range 30-85) and newly diagnosed BM were identified from a BM database. Clinical characteristics including survival times were retrieved from chart review. Diagnostic specific grade prognostic assessment (DS-GPA) was calculated based on clinical characteristics. Baseline TMT at diagnosis of BM was measured in MRI (axial plane of isovoxel 1x1x1mm), T1 – weighted images at diagnosis of BM.

Results: Median TMT was 5.4 mm (range 1.65 - 10.50 mm) and showed no correlation with age (correlation coefficient -0.34; p < 0.001 or Karnofsky performance status (correlation coefficient 0.213; p = 0.003), as well as no difference in dependence of cortisone treatment (p = 0.994) at BM diagnosis. Survival analysis using a Cox regression model was performed using baseline TMT diameters to predict survival time (HR 0.810; 95% CI 0.735-0.892; p < 0.001). Patients with a higher baseline TMT presented with an improved survival prognosis. In detail, risk of death was reduced by 19% with every additional millimeter of baseline TMT. Further analysis was performed by the means of a Cox regression model including TMT and DS-GPA as covariates (TMT HR 0.790; 95% CI 0.703-0.889; p < 0.001). DS-GPA HR 1.426; 95% CI 1.154-1.762; p = 0.001). In the multivariate model TMT prediction of survival was nearly unchanged with a reduced risk of death of 21 % with every additional millimeter of baseline TMT.

Conclusions: TMT, which can serve as a surrogate parameter of sarcompenia, is an independent predictor of survival in patients with newly diagnosed BM. TMT is easily and reproducibly assessable in routine MR images and may help to better define frail patient populations and may thus facilitate patient management by supporting patient selection for therapeutic measures or clinical trials.

Legal entity responsible for the study: Medical University of Vienna

Funding: Medical University of Vienna

Disclosure: All authors have declared no conflicts of interest.

331PD Phase II study of single agent ibrutinib in recurrent/ refractory primary (PCNSL) and secondary CNS lymphoma (SCNSL)

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Background: PCNSL is an aggressive primary brain tumor. Outcome and treatment options are poor for recurrent/refractory (r/r) disease. Response rates (ORR) range between 30-60% with a progression free survival (PFS) of 2-5 months. Ibrutinib has shown promising clinical response in some B-cell malignancies. This trial investigates ibrutinib in patients with r/r PCNSL and SCNSL.

Methods: Eligible patients had r/r PCNSL or SCNSL, age ≥ 18, ICG ≥ 2, normal end-organ function, and unrestricted number of CNS directed prior therapies. Ibrutinib was administered orally at 240 mg daily for 28 days followed by 14 days off. Dose adjustments were made according to hematological toxicities.

Results: 16 patients were enrolled (11 patients with PCNSL, 3 with SCNSL, 2 with r/r PCNSL and SCNSL). No complete responses were observed and 1 partial response was documented. Median PFS was 2.5 months (range 1.2-8.5 months) and median OS was 6.3 months (range 1.9-10.6 months). Prophylactic cranial irradiation (PCI) and salvage strategies were used in 4 patients with r/r PCNSL or SCNSL. All patients experienced adverse events including CNS toxicities (2/16 patients). 8 patients (50%) developed grade 3-4 de novo hematologic toxicities with severe thrombocytopenia and neutropenia. 1 patient with r/r PCNSL died due to multiorgan failure.

Conclusions: Ibrutinib has shown promising clinical activity in patients with primary and secondary CNS lymphomas but more investigation is required.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Results: Twenty patients were enrolled (3 at 560 mg, 17 at 840 mg). Median age was 69 (range 21-85); 12 were women. Median ECOG was 1 (0-2, 1, 1, 12, 2, 6). 65% had PCNSL and 35% SCNSL. 70% had recurrent disease. Eleven had parenchymal disease, 3 isolated cerebrospinal fluid (CSF) involvement and 6 both. The median prior CNS directed therapy was 2, all methotrexate regimens. Despite clinical and radiographic response, 2 patients withdrew and 1 stopped due to toxicity (fungal infection). Four grade 4 toxicities were observed in 4 patients (lymphopenia (2), sepsis (1), neutropenia (1)). Ten patients developed grade 3 toxicities, including lymphopenia in 3 patients, thrombocytopenia in 2, hyperglycemia in 2, lung infection in 2, neutropenia in 1, uraemic tract infection in 1, colitis in 1, and fungal encephalitis in 1. The most common toxicities were hyperglycaemia, anemia, and thrombocytopenia. After a median follow-up of 147 days, 16/20 patients were evaluated for response: CR 3 (CSF in 3; in the parenchyma), 9 PR, and 3 PD. 83% (13/20) ORR. In 3 patients response has not been confirmed in a 2nd assessment. The median PFS is 5.5 months (longest: 13.2 months). The mean Ibrutinib concentration in the CSF a day and 23 was 17 ± 15 ng/mL (3.97 ± 2.51 ng/mL). The CSF Ibrutinib concentrations reached in patients who are above the IC50 were required in vitro to reduce growth of lymphoma cells. Molecularly, a unique approach to the genetic alterations and outcome.

Conclusions: Patients with CNS lymphoma tolerate Ibrutinib with manageable toxicities. Ibrutinib might be a therapeutic alternative that should be further investigated in r/r CNS lymphoma patients.

Clinical trial identification: NCT02153526

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center

Funding: Pharmacy

Disclosure: All authors have declared no conflicts of interest.

The pharmacokinetics of methotrexate with and without rituximab in the treatment of primary central nervous system lymphoma (PCNSL)

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Background: PCNSL is a rare B-cell lymphoma. Most chemotherapy regimens are methotrexate (MTX) based, but recently have included Rituximab (R). MTX pharmacokinetics (PK) are highly variable and may correlate with patient (pt) outcome. However, the effect of R on MTX PKs has not been well characterised. We aimed to compare MTX PKs in pts treated with and without R.

Methods: We conducted a retrospective study of the PCNSL database at the National Neuro-Oncology Centre in Dublin, Ireland. Pts received MTX (3.5g/m2)/ Procarbazine/Vinristine (MTX group), or MTX/Procarbazine/ Vinristine + Rituximab (R-MTX). From written and electronic medical records, the following data were collected: pt demographics, creatinine clearance (CrCl), MTX dose escalation in folinic acid and changes in CrCl. Correlation of MTX PKs with survival is ongoing. Table 1: Mean MTX Level Over Time

<table>
<thead>
<tr>
<th>Hours</th>
<th>48</th>
<th>72</th>
<th>96</th>
<th>120</th>
<th>144</th>
<th>180</th>
<th>216</th>
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</thead>
<tbody>
<tr>
<td>MTX</td>
<td>3.68 (1.06)</td>
<td>0.56 (1.03)</td>
<td>0.62 (1.00)</td>
<td>3.52 (1.06)</td>
<td>0.62 (1.00)</td>
<td>3.52 (1.06)</td>
<td>0.62 (1.00)</td>
</tr>
<tr>
<td>95% CI</td>
<td>3.73 (1.10)</td>
<td>0.62 (1.00)</td>
<td>0.62 (1.00)</td>
<td>3.52 (1.06)</td>
<td>0.62 (1.00)</td>
<td>3.52 (1.06)</td>
<td>0.62 (1.00)</td>
</tr>
<tr>
<td>Mean</td>
<td>3.68 (1.06)</td>
<td>0.56 (1.03)</td>
<td>0.62 (1.00)</td>
<td>3.52 (1.06)</td>
<td>0.62 (1.00)</td>
<td>3.52 (1.06)</td>
<td>0.62 (1.00)</td>
</tr>
<tr>
<td>SD</td>
<td>0.74 (0.86)</td>
<td>0.84 (0.70)</td>
<td>0.84 (0.70)</td>
<td>0.84 (0.70)</td>
<td>0.84 (0.70)</td>
<td>0.84 (0.70)</td>
<td>0.84 (0.70)</td>
</tr>
<tr>
<td>Values</td>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Conclusions: This retrospective study in this rare cancer suggests that R may prolong MTX clearance. This may have implications for optimum MTX dosing and prognosis. Legal entity responsible for the study: Cancer Clinical Trials and Research Unit, Beaumont Hospital, Dublin, Ireland. Funding: Cancer Clinical Trials and Research Unit, Beaumont Hospital, Dublin, Ireland. Disclosure: All authors have declared no conflicts of interest.

IMRT and temozolomide for grade III glioma: Clinical and prognostic factors

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Background: To evaluate grade III gliomas treated in the era of IMRT and concurrent plus adjuvant Temozolomide (TMZ) with early clinical outcome and prognostic factors with quality of life.

Methods: 53 patients with anaplastic oligodendroglioma(25), anaplastic astrocytoma (18) and anaplastic oligoastrocytoma(10) treated with IMRT and concurrent (99%) and adjuvant TMZ (90%) were analyzed. 1p19q co-deletion data was available for 13 patients. 80% had KPS at least 90 with 30% seizure at presentation. Postoperative MRI was available in 63% cases and IMRT dose was 60 Gy in 30 fractions. First post treatment imaging was performed at 1 month and then at 3 months and 6 months post IMRT and then every 3 months. EORTC quality of life scale C35 and BN 20 was administered before starting IMRT, at completion and then at each follow up. Kaplan-Meier analysis was used to estimate disease free survival (DFS), overall survival (OS) and analysis was done using SPSS version 18.0

Results: The median follow-up was 25 months with 2 year DFS and OS were 75% and 88%. Patients tolerated treatment well with only 5% symptomatic CNS and 8% systemic toxicities. Ibrutinib was 95% completed concurrent TMZ schedule. At 1st evaluation, 30.4% had complete response, at 3 months 40% and at 6 months 43.5% At 6 months only 4% had progressive disease. Llast follow up 46/53 patients were evaluable with 8 deaths and 55% having stable to complete response. On univariate analysis OS was significant for DFS, KPS at presentation < 90 (p = 0.001) and response at 6 months (p = 0.02) were significant and for OS KPS at presentation (p = 0.004) alone. Gross total resection, no residual at postoperative MRI, 6 to 8 cycles of adjuvant TMZ, complete response at 6 months were favorable in terms of both DFS and OS. Histopathological types were not significant for DFS and OS and only 3 patients were 1p19q co-deletion positive. Quality of life scales suggested decline in mood, cognition, fatigue and toileting control initially and improvement beyond 3 months. There were no significant late effects till last follow up.

Conclusions: IMRT with TMZ among grade III glioma patients resulted in minimum treatment related toxicities and better quality of life with encouraging results. Proper case selection with future molecular prognostic markers will determine most favourable groups.

Legal entity responsible for the study: Medanta The Medicity, Gurgaon

Funding: Medanta The Medicity, Gurgaon

Disclosure: All authors have declared no conflicts of interest.

Treatment outcome in medulloblastoma with the POG 9031 protocol: a single institution review

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Background: The aim of the present study was to identify the various clinicopathological features and treatment outcome of cases of medulloblastoma who had received concurrent Chemoradiotherapy post operatively and treated as per the POG 9031 protocol at a tertiary care centre.

Methods: Medical records were reviewed to identify patients of Medulloblastoma who were treated between January 2005 and January 2015 at our centre. Data was gathered on demographics, clinical presentation, tumor characteristics, chemotherapy & radiotherapy protocols, adverse event and survival. The Chang Harisdiadis system was used for staging. Patients were classified as either poor risk (T3b-T4, M1 or > 1.5 cm4residual tumor) or standard risk disease (1p-3a, M0 and < 1.5 cm4residual tumor). The prognostic value of age, sex, risk category, Histopathological variants were assessed by univariate analysis using the log-rank test. Survival analysis was done using the Kaplan Meyer method.

Results: A total of 31 patients were included in the study. Seventy one percent of our patients (22/31) were in the Standard risk group (55% in the high risk group). The mean age of the study population was 9 years. The treatment protocol followed was Surgery followed by Craniospinal Irradiation followed by Chemotherapy as per the POG9031 protocol. Of the 31 patients who underwent Surgery, 27 had a Gross total resection. In the cohort of DFS, 4 patients had severe toxicities necessitating withdrawal of treatment. Fifteen patients (48%) were found to have some cognitive decline on follow up. The median follow up period was 48 months (12–108 months). The 5 year survival estimated from the Kaplan Meier curve was 74 %. Parameters like Age, sex, size of the lesion, Ki67 and Histopathological variant had no significant impact on the survival outcome, however a significant correlation was seen with the risk status (Median PFS 30 months vs 12 months in the standard risk and poor risk respectively).

Conclusions: Based on our data, we found that our schedule of medulloblastoma treatment was well tolerated. The 5 year survival of 70% seen with our treatment schedule is at par with that seen in existing literature. The neurocognitive decline seen in 48% of our patients is in keeping with existing data.
Annals of Oncology

Legal entity responsible for the study: Amrita Institute of Medical sciences
Funding: Amrita Institute of Medical Sciences
Disclosure: All authors have declared no conflicts of interest.

335P Phase II study of single agent buparlisib in recurrent/refractory primary (PCNSL) and secondary CNS lymphoma (SCNSL)
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Background: PCNSL is an aggressive primary brain tumor. Outcome and treatment options are poor for patients with recurrent/refractory disease. Response rates range between 30-60% with a progression free survival (PFS) of 2-6 months. PI3K inhibition, in particular of the delta isoform, has shown promising clinical response in some B-cell malignancies. This phase II trial investigates the pan-PI3K inhibitor Buparlisib in patients with recurrent/refractory T(r) PCNSL and SCNSL.

Methods: Eligible patients had T(r) PCNSL/SCNSL, age ≥ 18, KPS ≥ 50, normal end-organ function, and unrestricted number of prior therapies. In patients with SCNSL, systemic disease needed to be absent. Enrolled patients received Buparlisib 100 mg daily. The trial was closed prematurely due to limited clinical response.

Results: Four patients were enrolled at age 55, 60, 68, and 79 with a KPS of 90, 100, 90 and 60, respectively. Three were men. None had prior PCNSL. All had parenchymal disease. Median prior CNS directed treatment was 2 (range 1-3), all methotrexate regimens. Two grade 4 toxicities (luphoria and neutropenia) were observed that resolved after drug was held. The most common toxicities observed were hyperglycemia, thrombocytopenia, and lymphopenia. The overall response rate was 25% with one partial response. This patient developed psychiatric symptoms within 8 weeks of treatment and drug was discontinued. Three patients developed neurologic symptoms at a median of 37 days after trial drug initiation. All were found to have disease progression. The median progression free survival was 39 days with a median overall survival of 196 days. Buparlisib concentrations were assessed on day 15 of drug treatment in plasma and CSF 2h after drug dosing. Mean plasma concentration was 1104ng/ml (range: 844-1610); mean CSF concentration 139.5ng/ml (82.9-205). CSF treatment in plasma and CSF 2h after drug dosing. Mean plasma concentration was ≥ 25% as one partial response. This patient developed psychiatric symptoms within 8 weeks of treatment and drug was discontinued. Three patients developed neurologic symptoms at a median of 37 days after trial drug initiation. All were found to have disease progression. The median progression free survival was 39 days with a median overall survival of 196 days. Buparlisib concentrations were assessed on day 15 of drug treatment in plasma and CSF 2h after drug dosing. Mean plasma concentration was 1104ng/ml (range: 844-1610); mean CSF concentration 139.5ng/ml (82.9-205). CSF concentration in the trial population (340mM; range 202-499) was below the IC50 observed to induce cell death in lymphoma cells in vitro (<500mM).

Conclusions: Patients with CNS lymphoma tolerate drug with acceptable toxicities. Treatment did not result in clinical response possibly due to CNS concentrations below 500mM. Buparlisib might also not have single agent activity in this disease.

Clinical trial identification: NCT02301364

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center.
Funding: Novartis.
Disclosure: All authors have declared no conflicts of interest.

336P Case report of the effective use of BRAF inhibitor vemurafenib in a patient with relapse of pleomorphic xanthoastrocytoma
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Background: Pleomorphic xanthoastrocytoma is a rare tumor of the brain. It is approximately 1% of the astrocytomas of the brain. In some cases, the tumor is well-demarcated and slow-growing with a favorable prognosis. At the same time reported cases of its malignant transformation with a poor prognosis. Most often this tumor occurs in a young age and manifest with epileptic syndrome. The main treatment is surgical. According to the literature, 30–40% of patients with pleomorphic xanthoastrocytoma detected mutation of V600E BRAF was.

Methods: The patient 25 years old in January 2011 revealed a tumor of the left occipital lobe of the brain. 22 Jan 2011 completed the removal of a brain tumor. Morphologically diagnosed as a pleomorphic xanthoastrocytoma with signs of anaplasia grade 3, Ki-67 - 15%. In the postoperative, in February-April 2012, conducted a course of radiation therapy to the left occipital lobe of the brain with total focal dose 60 Gy. In September 2014 after 2 years and 8 months after the operation revealed a relapse of a brain tumor. 25 Sep 2014 made the removal of the recurrent tumor. In December 2014 revealed a relapse of a brain tumor, 25 Sep 2014 made the removal of the recurrence of a brain tumor. In December 2014 marked the progression of the disease. Revealed continued tumor growth in the brain. The size of the recurrent tumor 4 x 3 cm. From December 2014 we started the targeted therapy with Vemurafenib. Achieved partial regression of the tumor in the brain. The size of residual tumors currently, less than 1 cm. Therapy with Vemurafenib lasts 1 year and 6 months.

Conclusions: Thus, the presence of the V600E BRAF mutation is another target for effective treatment of recurrences of pleomorphic xanthoastrocytoma. Further studies are needed for the study of BRAF inhibitors in patients with pleomorphic xanthoastrocytoma.
Background: Meningiomas comprise 24-30% of all tumors occurring in the central nervous system. Conventional morphologic studies as criteria in routine Hematoxylin and Eosin stained sections (H and E) may not be accurate in grading and assessing tumor histology. Therefore, we aimed at identifying a novel scoring system for the preoperative grading of meningiomas. MVD and the proliferative index are well known to be helpful in grading and prognosis of tumors. Angiogenesis is a key event in the spread of tumors and denotes a poor prognosis. Immunohistochemical staining was done for proliferative index with Ki-67 and for angiogenesis with CD34 antibodies. Statistical analysis was performed using Mann – Whitney U test. p value of < 0.05 was considered significant.

Methods: A total of 256 patients with newly diagnosed meningioma undergoing surgery from 2012 to 2014 were included in this study. Immunohistochemical staining was done for proliferative index with Ki-67 and for angiogenesis with CD34 antibodies. Statistical analysis was performed using Mann – Whitney U test. p value of < 0.05 was considered significant.

Results: There were 128 patients each in the high and low grade group. The mean age of the high grade group was 52.42 +/- 14.74 years and for low grade it was 47.86 +/- 10.77 years. 73% of patients had raised intracranial pressure and 18.4% of patients had raised intracranial pressure. The mean MVD was 49.67 +/- 22.35, 41.37 +/- 7.45 and 35.62 +/-4.44 in grade I, II and III tumors respectively which was statistically significant. (p< 0.01). The mean +/- SD MVD of 1st was 1.14 +/-0.84, 1.94 +/- 2.73 and 3.62 +/- 4.44 in grade I, II and III tumors respectively which was statistically significant. (p< 0.01). The mean +/- SD MVD was 49.67 +/- 22.35, 41.37 +/- 7.45 and 35.62 +/- 4.44 in grade I, II and III tumors respectively which was statistically significant. (p< 0.01). The mean +/- SD MVD was 49.67 +/- 22.35, 41.37 +/- 7.45 and 35.62 +/- 4.44 in grade I, II and III tumors respectively which was statistically significant. (p< 0.01).

Conclusions: MIB-1 LI is an important complementary tool to accurately grade meningotheal tumors and assess tumor biology. Specific cycling endothelial markers along with CD34 MVD could be used to assess the prognosis of these tumors. Legal entity responsible for the study: National Board of Examinations, New Delhi. Base Hospital, Delhi Cantt, New Delhi. Funding: Base Hospital Delhi Cantt, New Delhi. Disclosure: All authors have declared no conflicts of interest.
consistent. We sought to evaluate the clinical significance of EGFRvIII status and the EGFR overexpression in GBM among the Indian population, where potential targeted therapy may be the only hope.

**Methods:** A single centre, non-randomized, retrospective study with a prospective arm was done. All patients were treated at the Amrita Institute Of Medical Sciences, Kochi between Jan 2014 and August 2015. 40 patients were included, being the first of its kind in the Indian context the study was undertaken as a pilot.

**Results:** Results show expression of EGFRvIII had no correlation with the clinical outcome, OS 15.7 vs 24.6 months (p = 0.80), PFS 10 months vs 8 months (p = 0.520). However a significant number of patients expressed EGFRvIII (58%). Surprisingly, the majority of patients expressed the EGFR wild type, and EGFR exon 19 (57%) over-expression had a significantly negative impact on the clinical outcome, with an OS of 7.3 months vs 15.4 months and PFS 7.3 months vs 13 months (p = 0.001).

**Conclusions:** We found that a high percentage of GBM exhibit EGFR overexpression and amplification, as did a significant proportion expressing EGFRvIII. Our results represent a step forward for the identification of GBM patients in the Indian scenario who could respond to specific therapies targeting EGFR. This requires confirmation in independent larger data sets.

**Legal entity responsible for the study:** Amrita Institute of Medical Sciences

**Disclosure:** All authors have declared no conflicts of interest.

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**Table 344P**

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>Median OS (mo)</th>
<th>Range (mo)</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>15.7</td>
<td>8-24.6</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>3-18</td>
</tr>
<tr>
<td>AB</td>
<td>11.5</td>
<td>6-20</td>
</tr>
<tr>
<td>O</td>
<td>24.6</td>
<td>15.4-42</td>
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</table>

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**The role of ABO blood groups in glial neoplasia**

A. Alkan1, G. Yaciz2, M. Cengiz2, I. Celik2, A. Kars1, F. Zorlu2

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**Background:** There are numerous diseases that are claimed to have a correlation with ABO blood groups. The association with malignancy, especially with exocrine pancreas malignancy, has been documented. Analysis on distribution of blood groups in primary brain tumors and clinical value has revealed conflicting results. Here we aimed to evaluate the association between blood groups and glial neoplasia.

**Methods:** Patients admitted between 2000–2013 and had a diagnosis of glial neoplasia were evaluated. Documented blood groups were analyzed and compared with the National blood group frequencies. There was no statistically significant difference between all grades of glioma and healthy control patients. Median overall survival (mOS) of GBM patients are 12.9, 13.4, 5.7, 12.8 months in A, B, AB, and O blood groups, respectively (p = 0.46). mOS of anaplastic astrocytoma patients are 24.4, 13.4, 5.7, 13.4 months in A, B, AB, and O blood groups, respectively (p = 0.1). mOS of GBM patients are 12.9, 13.4, 5.7, 12.8 months in A, B, AB, and O blood groups, respectively (p = 0.1). mOS of anaplastic astrocytoma patients are 24.4, 13.4, 5.7, 13.4 months in A, B, AB, and O blood groups, respectively (p = 0.1). mOS of GBM patients are 12.9, 13.4, 5.7, 13.4 months in A, B, AB, and O blood groups, respectively (p = 0.1).

**Conclusions:** In our small patient group, when compared with general population, different blood groups are similar (p = 0.80).

**Legal entity responsible for the study:** Ankara University Medical School-Cebeo Hastanevi Tibiili Medecine, Ankara, Turkey

**Disclosure:** All authors have declared no conflicts of interest.

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**TERT as a prognostic factor for gliomas progression-free survival (PFS)**

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**Background:** High frequencies of TERT promoter mutations have been described in gliomas. This underlies telomeres maintenance upregulating telomerases. The mutation rate is higher in glioblastomas (GBM).

**Methods:** Observational and retrospective analysis of 100 patients with different histological types of gliomas. TERT mutations were determined by RT-PCR in brain tumor samples obtained from paraffin-embedded tissue. Survival analysis was performed with Kaplan-Meier curves compared by Log-Rank test.

**Results:** There were included 52% GBM, oligodendrogliomas (OO) 12% and astrocytomas (AA) 29% each, and oligoastrocytomas (OA) 7%. The highest rate of TERT mutation was achieved in the OO group (66.7%) followed by GBM (55.8%) and AA (27.6%). From the 46% patients with TERT mutation: GBM 63%, OO and AA each 17.4%. Median relapse/progression free survival was 37, 33 and 7 months for AA, OO, OA and GBM respectively if wild type TERT, while if mutated 14, 20 and 8 months. TERT and ATRX seem to be mutually exclusive as there were only 2% coincidences.

**Conclusions:** TERT mutations are determinant prognostic factors in glioma biology of both high and low grade.

**Legal entity responsible for the study:** Fundacion IRTP, Fundación Parc Salut Mar

**Disclosure:** All authors have declared no conflicts of interest.
A prospective analysis of quality of life (QoL), cognitive functions (CF) and psychological status (PSY) in glioblastoma (GBM) patients (PTS) treated with RT and temozolomide (TMZ)

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Background: GBM PTS can show changes in CF during the treatment which can affect their daily lives. We analyzed QoL, PSY and CF in these PTS treated with RT plus TMZ.

Methods: PTS with newly histologically diagnosed GBM treated with RT and TMZ as first-line therapy and KPS ≥ 60 were enrolled. We assessed QoL using EORTC QLQ-C30 and BN20. CF were evaluated with MMSE, and PSY with HADS test. Evaluations were performed at each radiological assessment: T0 (before treatment), T1 (1 month after RT + TMZ), T2 (6 ms from T0), T3 (9 ms from T0) and T4 (12 ms from T0). A repeated-measure linear mixed-model was used to estimate group differences over time and χ² test for compare mean values at each time.

Results: We enrolled 112 PTS, median age was 59; 69 PTS were male and 36 PTS aged ≥ 65. All PTS were treated with TMZ until disease progression. Role functioning (RF) statistically improved over time in female (p = 0.02) and PTS ≤65y (p = 0.05); emotional functioning improved (p = 0.02) at T4 versus T0 in all PTS; social functioning improved in PTS with lesions at left side hemisphere (LSH) (p < 0.05). Global Health Status (GHS) showed a trend for improving during the treatment and was statistically higher in PTS with LSH (p < 0.01). Motor dysfunction worsened over time (p < 0.05) and communication deficits was higher in PTS with LSH (p < 0.01); drowsiness improved in PTS with lesions at right site hemisphere (p < 0.01). Anxiety worsen in elderly PTS over time (p = 0.02) and the average score was higher in PTS with LSH. Depression worse only in males (p < 0.01). Average MMSE score was lower in elderly PTS (p = 0.01) and in PTS with LSH (p < 0.01). PTS with radiological progression disease reported statistically lower scores in RF (p < 0.01), GHS (p < 0.02), drowsiness (p < 0.05), anxiety (p < 0.01) and depression (p < 0.01), and MMSE (p < 0.01) versus PTS without radiological progression.

Conclusions: Some variables related to QoL, PSY and CF may improve during standard treatment with RT and TMZ in PTS with GBM. Moreover, age, gender and site of lesion might impact on specific factors. Radiological progression may correlate with worsening of specific points for QoL, PSY and CF.

Legal entity responsible for the study: IOV

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Characteristics of glioblastomas (GBM) not resected (only biopsy) homogeneously treated with Stupp regimen. Results from the GLIOCAT study

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Background: Prognosis of GBM is especially poor for unresected patients even when treated with the standard EORTC regimen.

Methods: We analyzed clinical characteristics, median progression free survival (PFS) and median overall survival (OS) of unresected patients from the database of the GLIOCAT study (432 patients uniformly treated with the EORTC regimen).

Results: Sixty-five patients began concurrent therapy. OS for all patients who started treatment was 7.2 months (95% CI 4.3-10.2). Fourteen patients could not even complete the concomitant phase (TMZ + RxT) (21.5%). Fifteen patients could not even complete the concomitant phase (TMZ + RxT) (21.5%). Fifty-one patients (78.5%) completed concomitant treatment and are described here. Median age 61 years old (29 males and 22 females). Multifocal tumor in 12 patients. Median lapsed time to start RT: 4 weeks. PFS was 6 months (95% CI 3.9-8.03) and OS was 9 months (95% CI 6.4-11.5). MGMT status was available for 31 patients. OS and PFS were 12 months (95% CI 9.5-14.7) and 7 months (95% CI 3.8-10.4) for mMGMT vs 7 months (95% CI: 5.2-9.7) for mMGMT status (95% CI: 1.1-12.8) and 5 months (95% CI: 3.2-6.7) for mMGB (NS). Only age (older than ≥ 50) emerged as a poor prognostic factor: OS (95% CI: 5.7-10.2) vs. 19 (95% CI: 9.4-28.5), P < 0.05. Treatment at recurrence was administered to 28 patients (50.7%). OS and PFS for these patients was 18 months (95% CI: 13.3-23.0) and 7 months (95% CI: 5.9-8.0), respectively, compared with 6 months (95% CI: 5.0-6.9) and 4 months (95% CI: 1.6-6.3) for patients without a second line treatment.

Conclusions: Median OS for unresected patients treated with the standard treatment is similar to that reported in the pivotal trial. However, 21.5% could not even complete concurrent therapy, and only 30.7% could receive a second line therapy.

Legal entity responsible for the study: GLIOCAT

Funding: GLIOCAT

Disclosure: All authors have declared no conflicts of interest.
Extended adjuvant temozolomide as prognostic factor of longer overall and progression-free survival in glioblastoma multiforme


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Background: Glioblastoma multiforme (GBM), the most common malignant primary central nervous system tumour, has significant morbidity-mortality. The aim is to determine prognostic factors (PF) of overall survival (OS) and progression-free survival (PFS) in patients treated with Stupp protocol.

Methods: Retrospective analysis of GBM patients 21 years, diagnosed from March 2004 to December 2014, treated with radiotherapy (RT) plus concomitant and adjuvant temozolomide (aTMZ). OS and PFS were assessed by Kaplan-Meier and multivariate analysis (MA) was performed using Cox regression.

Results: A total of 221 patients completed the concomitant TMZ-RT and were included in final analysis. Majority were males (n = 134), with median age of 61 years old (24-84) and 43.1% ECOG performance status 0. Gross total resection (GTR) was possible in 46.9%, partial resection in 33.3% and stereotactic biopsy (SB) in 19.7%. 197 patients proceeded to TMZ. 107 suspended ≥ 6 cycles, 17 suspended on 6th cycle due to progression, 13 performed 6 cycles of programmed TMZ, 60 extended until progression (44 to 7-12 cycles and 16 over 12 cycles). Median OS was 15 months (CI 95%, 13.4-16.6) and PFS 8 months (CI 95%, 7.0-9.0). The PF for longer OS were: prog < 0.001; GTR (HR = 0.5) and PTS receiving a second-line chemotherapy (HR = 0.7) were positive prognostic factors in terms of OS.

Conclusions: In our real-life experience most PTS underwent surgery, performed a second-line chemotherapy, although a subset of PTS had a poor performance status. However, we reported a good clinical outcome demonstrating the importance of molecular characterization in these PTS. Type of surgery, ECOG PS, MGMT methylation and lines of chemotherapy were independent prognostic factors for better OS.

Legal entity responsible for the study: IUV

Funding: None

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Functional status of central nervous system in intensive radiotherapy for brain metastases

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Background: Combined treatment including whole brain irradiation (WBI) with additional boost has shown its advantages concerning overall survival of patients with solitary brain metastasis (SBM). However, the literature data on neurotoxicity and safety of additional local irradiation are ambiguous. The purpose of the study was to compare electrophysiological parameters of the functional state of the brain after WBI and WBI with additional boost to the bed of removed metastatic foci.

Methods: The study included 16 patients of each gender with SBM after the treatment of primary tumors. Parameters of EEG and electrical conductivity (EC) of auricular surface points (AP) were studied in two groups of patients receiving irradiation 3-4 weeks after metastasis removal: the control group (WBI) and the main one (WBI + boost). EEG
was recorded monopolarly using Encephalan EEG-19/26, Russia (26 channels) from 19 electrodes according to the international 10-20 system. Power spectrum values before and after radiation therapy (RT) were compared using MANOVA. ECAP were studied using DuaDENS PC medical diagnostic system at the same RT stages.

Results: The main group showed increased power values of 0 range by 6-9% (p < 0.05), compared with the initial values, at F3, F4, C3, C4, after RT, as well as decreased u values by 10-13% (p < 0.05) at O2, T3. Analysis of EC in AP of the nervous system demonstrated primary transition to the hypofunction during RT, which was more marked in the main group: in AP associated to the cerebral cortex, dynamics of decrease of functional activity in the structure was noted 2.4 times more often than in WBI.

Conclusions: EEG and electroacupuncture parameters showed the decrease in CNS functional activity during increased radiation exposure due to the additional boost. The data suggest the need for development of bioadaptive effects weakening the damaging effects of adjacent RT in patients with brain metastasis.

Legal entity responsible for the study: Rostov Research Institute of Oncology

Funding: Ministry of Health of the Russian Federation

Disclosure: All authors have declared no conflicts of interest.

3SS3P Metformin as an adjuvant anticancer therapy in the treatment of high grade glioma

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Background: Despite standard treatment with surgery and temozolomide (TMZ) and radiotherapy, the prognosis of high grade glioma (HGG) remains dismal. Metformin, an anti-diabetic drug has demonstrated anti-tumor effects in gliomas. Interestingly, a recent transcriptomic analysis showed that interleukin 13 receptor alpha 2 (IL-13Rα2) is highly upregulated in patients with diabetic nephropathy. IL-13Rα2 is also commonly overexpressed in HGG. However, the effect of metformin on IL-13Rα2 expressing glioma cells is currently unknown. Hence, we aim to evaluate the combined treatment of TMZ and metformin in a series of human glioma cells with IL-13Rα2, and other commonly found genetic aberrations for translational purpose.

Methods: A series of human glioma cell lines were treated with TMZ, metformin and a combination of TMZ and metformin (15 μM). The overexpression of IL-13Rα2 in glioma cells could confer resistance against metformin through the enhanced activation of AMPK and Akt pathways. Neither TMZ nor metformin alone induced cell death. The activities of these drugs where examined by performing western blotting analyses. Analysis was performed using GraphPad Prism.

Results: IL-13Rα2 positive glioma cells were resistant to metformin in a dose-dependent manner. The combination of TMZ and metformin markedly overexpressed IL-13Rα2 in glioma cells compared to IL-13Rα2-null glioma cells. Furthermore, in the combined treatment group, metformin effectively inhibited Akt and mTOR activation induced by TMZ. There was no significant reduction in mTOR and S6K phosphorylation in the combined versus metformin group.

Conclusions: Metformin sensitizes TMZ-resistant cells to increased cell death. The combination of TMZ and metformin markedly overexpressed IL-13Rα2 in glioma cells which is associated with resistance against metformin.

Legal entity responsible for the study: Dawn Chong

Funding: National Medical Research Council

Disclosure: All authors have declared no conflicts of interest.

3SP4P Phase II study of atorvastatin in combination with radiotherapy and temozolomide In patients with glioblastoma (ART): interim analysis report

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Background: Glioblastoma (GBM) is the commonest primary brain tumour in adults and it carries the worst prognosis. Atorvastatin is an inhibitor of HMG-CoA reductase, a rate limiting enzyme in the mevalonate pathway. Preclinical studies demonstrate encouraging anticancer activity of atorvastatin.

Methods: In this open-label, prospective, single-arm, phase II study, eligible patients received oral Atorvastatin (40 mg/d for 3 weeks and 80 mg/d thereafter) in combination with standard therapy comprising radiotherapy (40 Gy/30 fractions) and TMZ (75 mg/m²/d) in the 6-week concurrent phase, then with TMZ (100-200 mg/m²/d on days 1-5 for 6 cycles). The primary endpoint is progression free survival (PFS) at 6 months. A minimum of 80% power required at least 32 eligible patients with planned interim analysis after the first 15 evaluable patients.

Results: From January 2014, 20 of 32 planned patients have received therapy and the first 15 evaluable patients were included in this planned interim analysis. Median age was 48 (20-69); 28% were ≥60 years of age and 61% were male. 95% of patients underwent resection and 5% had biopsy only. Patients had median and minimum follow-up of 1.6 months and 6 months, respectively. PFS-rate was 67% with median PFS of 9.1 months. Median overall survival has not yet been reached to date. Grades 3 and 4 hematological adverse events occurred in 33% of patients. Three patient died due to disease progression.

Conclusions: This is the first clinical trial investigating atorvastatin in combination with standard therapy (RT and TMZ) in newly diagnosed GBM patients. Planned interim analysis appears promising and it met criteria for continued accrual. To date, the treatment was safe in this patient population. Clinical trial information: NCT01209573

Clinical trial identification: NCT01209573

Legal entity responsible for the study: Ministry of Health, Saudi Arabia

Funding: King Fahad Medical City

Disclosure: All authors have declared no conflicts of interest.

3S51P METIS: A phase III study of radiosurgery with TTFields for 1-10 brain metastases from NSCLC

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Background: Tumor Treating Fields (TTFields) are a novel, non-invasive and anticancer treatment modality, based on low intensity alternating electric fields. Efficacy of TTFields in non-small cell lung cancer (NSCLC) has been demonstrated in multiple in vitro and in vivo models, and in a phase II clinical study. TTFields treatment to the brain was shown to be safe and effective in glioblastoma patients.

Trial design: 270 patients with 1-10 brain metastases (BM) from NSCLC will be randomized in a ratio of 1:1 to receive stereotactic radio surgery (SRS) followed by either TTFields or supportive care alone. Patients are followed-up every two months until 2nd cerebral progression. Patients in the control arm may cross over to receive TTFields at the time of 1st cerebral progression. Objectives: To test the efficacy, safety and neurocognitive outcomes of TTFields in this patient population. Endpoints: Time to 1st cerebral progression (primary), time to neurocognitive failure based on the following tests: HVLT, COWAT and TMT; overall survival; radiological response rate, quality of life, adverse events severity and frequency (secondary). Treatment: Continuous TTFields at 150 kHz will be applied to the brain within 7 days of SRS. The treatment system is a portable medical device allowing normal daily life activities. The device delivers TTFields to the brain using 4 Transducer Arrays, which may be covered by a wig or a hat for cosmetic reasons. Patients will receive the best standard of care for their systemic disease. Statistical Considerations: This is a prospective, randomized, multicenter study for 270 patients. The trial is designed to detect an increase in the time to cerebral progression from 7.7 to 13.4 months (hazard ratio 0.57). This sample size assessment takes into consideration a competing risk (death prior to cerebral progression) of 0.8R252 per month in both treatment arms. The competing risk is based on a predicted median overall survival of 8.4 months mainly due to systemic disease progression. The trial has 80% power at a two sided alpha of 0.05. The sample size was calculated using a log-rank test (based on Lakatos 1998 and 2002).

Legal entity responsible for the study: FDA

Funding: Novocure Ltd.

Disclosure: All authors have declared no conflicts of interest.

3S64P A randomized phase 2, single-blind study of temozolomide (TMZ) and radiotherapy (RT) combined with nivolumab or placebo (PBO) in newly diagnosed adult patients (pts) with tumor O6-methylguanine DNA methyltransferase (MGMT)-methylated glioblastoma (GBM) – CheckMate-548

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Background: GBM, the most common adult primary brain tumor, has an aggressive clinical course and a poor prognosis. Approximately 40% of pts with GBM have tumors with a methylated MGMT gene promoter, which is associated with DNA repair. In these pts, TMZ may induce DNA damage and cell death due to silencing of
the MGMT promoter, a mechanism potentially augmented by combination with checkpoint inhibitors. Nivolumab, a fully human IgG4 monoclonal antibody to the programmed death-1 receptor, has demonstrated overall survival (OS) benefit in the treatment of metastatic melanoma, non-small cell lung cancer, and advanced renal cell carcinoma. CheckMate-548 (NCT02667587) is a phase 2, randomized, single-blind study evaluating the efficacy and safety of TMZ/RT ——> TMZ with nivolumab or PBO in pts with newly diagnosed MGMT-methylated GBM. In a companion phase 3 trial (CheckMate-498, NCT02617589), eligible pts with MGMT-unmethylated tumors (N = 550) will be randomized to receive nivolumab + RT followed by nivolumab, or TMZ/RT ——> TMZ, with OS as the primary endpoint.

**Trial design:** Eligibility criteria include newly diagnosed, histologically confirmed supratentorial GBM in pts aged ≥ 18 years with Karnofsky performance status ≥ 70, and a tumor test result that shows a MGMT methylated, partially methylated, or indeterminate methylation type. Pts previously treated for GBM other than by resection and those with recurrent or secondary GBM are ineligible. Approximately 320 pts, stratified by partial or complete resection, will be randomized 1:1 to receive TMZ/RT ——> TMZ in combination with nivolumab or PBO. Treatment will continue until disease progression or unacceptable toxicity. The primary objective is OS in pts treated with TMZ/RT ——> TMZ and nivolumab versus TMZ/RT ——> TMZ and PBO; the secondary objective is progression-free survival. Select exploratory objectives include safety, biomarker analyses, and neurocognitive outcomes. In the follow-up period, safety and tolerability, tumor progression, and survival will be evaluated.

**Legal entity responsible for the study:** Bristol-Myers Squibb

**Funding:** Bristol-Myers Squibb

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DLYE5953A is a humanized IgG1 anti-Ly6E monoclonal antibody conjugated to the potent anti-mitotic agent monomethyl auristatin E (MMAE), linked through the protease-labile linker MC-vc-PAB. DLYE5953A has the potential to selectively target Ly6E-expressing cancers.

Methods: This open-label, 3 + 3 dose-escalation study assessed safety, tolerability, pharmacokinetics (PK), and preliminary anti-tumor activity (RECIST v1.1) of DLYE5953A administered intravenously every 21 days (q3w) in pts with locally advanced or metastatic solid malignancies that had progressed on standard therapy. Tumor Ly6E expression was assessed by FHC and qRT-PCR.

Results: As of 31 December 2015, 57 pts, median age 57 (range 33-82), received a median of 4 cycles of DLYE5953A (range 1-14). Escalating doses of DLYE5953A (0.2-2.4 mg/kg) were tested in 20 pts. No dose limiting toxicities were identified. The median of 4 cycles of DLYE5953A (range 1-14). Escalating doses of DLYE5953A (+) or 30 mg CEA-IL-2v (4 pts CEA + ; 4 pts CEA-). Accumulation of 89Zr-CEA-IL-2v was observed in a dose-dependent manner and role of IL-2 receptor-binding.

Conclusions: At all doses, 89Zr-CEA-IL-2v accumulated in spleen and secondary lymphoid tissues like spleen (SUVmean 10.0 ± 3.1) and non-pathological lymph nodes (SUVmean 2.0 ± 1.2) at all doses; this was considered IL-2 receptor-meditated uptake. Intratumoral accumulation of 89Zr-CEA-IL-2v in cycle 1 was observed in CEA+ patients: 1/4 pts at 20 mg and 4 pts at 30 mg (SUVpeak 5.4), 6/8 pts at 20 mg (SUVpeak 5.2 ± 2.7) and 4/4 pts at 30 mg (SUVpeak 4.0 ± 1.1). At cycle, 89Zr-CEA-IL-2v accumulation in tumor lesions (SUVpeak 4.0 ± 1.1) decreased, possibly due to anti-drug antibodies or expansion of IL-2R expressing T-cells. In tumors with high accumulation of 89Zr-CEA-IL-2v at cycle 1, there was a trend towards decreased metabolic activity at early FDG-PET evaluation.

Background: CEA-IL2v (cetuximab amunaleukin, RG7813) is an engineered IL-2 variant (IL-2v) antibody directed against Carcinoembryonic Antigen (CEA) with abolished IL-2 receptor (IL-2R) α (CD25) binding. The molecule was designed to improve the pharmacological and safety profile of IL-2 and direct local accumulation in CEA-positive (CEA+) tumors. To demonstrate selective and specific tumor targeting, CEA-IL-2v was labeled with 89Zr. Biodistribution and tumor accumulation was assessed at varying doses in tumors with different CEA status.

Methods: Patients (pts) with advanced and/or metastatic solid CEA+ or CEA-negative (CEA-) tumors were eligible for this sub-study of a phase I trial. CEA-IL2v was administered intravenously q2W at total doses of 6 mg, 20 mg and 30 mg (incl 50 MBq/2mg 89Zr-CEA-IL2v). All pts underwent up to 3 89Zr-PET assessments during cycle 1. In the 20 mg cohort, pts with initial tumor uptake at cycle 1 underwent additional 89Zr-PET assessments in cycle 4.

Results: Patients were treated with 6 mg (4 pts CEA + ; 3 pts CEA-), 20 mg (8 pts CEA+) or 30 mg CEA-IL2v (4 pts CEA + ; 4 pts CEA-). Accumulation of 89Zr-CEA-IL-2v (at day 5 post injection) was observed independent of CEA status in lymphoid tissues like spleen (SUVmean 5.4 ± 2.2) and non-pathological lymph nodes (SUVmean 2.4 ± 1.1) at all doses; this was considered IL-2 receptor-meditated uptake. Intratumoral accumulation of 89Zr-CEA-IL-2v in cycle 1 was observed in CEA+ patients: 1/4 pts at 20 mg and 4 pts at 30 mg (SUVpeak 5.4 ± 2.0). At cycle 4, 89Zr-CEA-IL-2v accumulation in tumor lesions (SUVpeak 4.0 ± 1.1) decreased, possibly due to anti-drug antibodies or expansion of IL-2R expressing T-cells. In tumors with high accumulation of 89Zr-CEA-IL-2v at cycle 1, there was a trend towards decreased metabolic activity at early FDG-PET evaluation.

Conclusions: At all doses, 89Zr-CEA-IL-2v accumulated in spleen and secondary lymphoid tissues, due to IL-2 mediated uptake. CEA-mediated tumor accumulation was observed in a dose-dependent manner with consistent targeting starting at 20 mg CEA-IL-2v; a phase I study as monotherapy and with atezolizumab is ongoing.
**Annals of Oncology**

**355C** First-in-human study of AC0010, a novel irreversible, mutant-selective EGFR inhibitor in patients with 1st generation EGFR TKI-resistant non-small cell lung cancer (NSCLC)

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Background: AC0010 (Avitinib) is a third generation irreversible EGFR inhibitor. Overcoming T790M-induced resistance by AC0010 has been demonstrated in preclinical studies. This is a first-in-human dose escalation study of AC0010 in EGFR-TKIs resistant patients (NCT02274337).

Methods: NSCLC patients with EGFR positive mutation who developed resistance to the 1st generation EGFR TKIs were enrolled including both T790M positive and negative patients. Patients were orally administrated with AC0010 capsules in total 8 dose cohorts: 6 QD dose cohorts (50 mg QD, 100 mg QD, 200 mg QD, 350 mg QD and 550 mg QD), and 3 BID dose cohorts (175 mg BID, 250 mg BID and 380 mg BID). All patients were assessed for pharmacokinetics (PK), overall response rate (ORR), disease control rate (DCR), and adverse events (AEs). Prior to the treatment, tumor biopsy for genotyping was required to confirm the T790M status.

Results: As of 5 May 2016, 51 patients (26/25 (49%) female, median age 55, 44.7% (86%) T790M positive or wild type) were enrolled. Maximum tolerated dose has not been reached. Most of AEs were grade 1 and transient. Common drug related AEs zgrade 3 were rash (4%), ALTAST elevation (4%) and Pneumonia(2%). No hyperglycemia and grade 3 QTc prolongation were observed. PK was dose proportional, median plasma half-life was 7.8 (7.6-8.0) hours. BID dosing method could reduce fluctuation coefficient of plasma concentration by 0.40 fold, and improve AUC by 1.28 fold, compared to QD dosing, and no food effects were seen. Among all evaluated patients at the data cut-off, ORR was 41.7% (20/48), and DCR was 75.6% (36/48). Responses were observed at dose levels ≥200mg QD. In AC0010 dose level 2 (250mg QD), the ORR was 57.6% (19/33) and DCR was 87.9% (29/33), and BID dosing schedule had better ORR (66.7% vs 33.3%) and DCR (94.4% vs 77.8%) than QD dosing schedule. The longest duration of response was ≥11 months at data cut-off.

Conclusions: AC0010 demonstrates a safety profile and promising antitumor activity for NSCLC patients with T790M mutation who develop the resistance to 1st generation TKIs.

Clinical trial identification: NCI/clinicalTrials.gov number: NCT02274337

Legal entity responsible for the study: Zhangi

Funding: ACEA Pharmaceutical Research, Hangzhou, China, and ACEA Biosciences Inc. San Diego, USA.

Disclosure: All authors have declared no conflicts of interest.

**361PD** Interim results from the completed first-in-human phase I dose escalation study evaluating MP0250, a multi-DARPin® blocking HGF and VEGF, in patients with advanced solid tumors

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Background: DARPins® (designed ankyrin repeat proteins) are small proteins that can be engineered to bind to specific targets with high specificity and affinity. MP0250 is a first-in-class, tri-specific multi-DARPin® neutralizing VEGF and HGF as well as binding to human serum albumin to increase pharmacokinetic levels by 350mg cohort, the ORR was 57.6% (19/33) and DCR was 87.9% (29/33), and BID dosing schedule had better ORR (66.7% vs 33.3%) and DCR (94.4% vs 77.8%) than QD dosing schedule. The longest duration of response was ≥11 months at data cut-off.

Conclusions: AC0010 demonstrates a safety profile and promising antitumor activity for NSCLC patients with T790M mutation who develop the resistance to 1st generation TKIs.

Clinical trial identification: NCI/clinicalTrials.gov number: NCT02274337

Legal entity responsible for the study: Zhangi

Funding: ACEA Pharmaceutical Research, Hangzhou, China, and ACEA Biosciences Inc. San Diego, USA.

Disclosure: All authors have declared no conflicts of interest.

**359C** TAX-TORC: An investigator initiated phase I study combining the dual mTORC1/2 inhibitor AZD2014 in combination with weekly paclitaxel in high-grade serous ovarian cancer

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Background: We previously evaluated the tolerability of AZD2014 administered with weekly paclitaxel in 2 intermittent schedules. Based on the preliminary activity and preclinical data, we aimed to confirm tolerability in high-grade serous ovarian cancer (HGSOC), document preliminary efficacy and evaluate biomarkers of resistance and sensitivity.

Methods: Patients with HGSOC were treated with oral AZD2014 (50mg BD) for 3 days on/4 days off with weekly paclitaxel (80mg/m²) for 6 weeks of a 7 week cycle. Archival tumour samples are being assessed by targeted next-generation sequencing to identify potential biomarkers of sensitivity and resistance. Circulating plasma DNA assessments are being performed at baseline, at the end of cycle 1, at maximum response and at relapse.

Results: Currently 20/25 patients have been recruited with a median age of 67 years. The median number of previous treatments is 3 and 18/20 patients (90%) were platinum resistant or refractory prior to trial entry. Nineteen of the twenty patients (95%) received prior paclitaxel, of whom 3/20 (15%) received weekly paclitaxel. All 20 patients were assessed for toxicity, the most common grade 3-4 toxicities seen were vomiting (3/20), diarrhoea (2/20) and respiratory infections (2/20). There were 2 cases of pneumonitis (grades 1 and 3) and one case of bowel perforation which occurred at the site of metastatic infiltration, in the context of a rapidly reducing CA125 response. Twelve patients were evaluable for RECIST response at the end of cycle 1, after 6 weeks of combination therapy, 7/12 (58%) showed a partial response. Of 14 patients with evaluable CA125, 10 (71%) had a 50% reduction in baseline values. Of the patients that had previously received weekly paclitaxel, 2/3 (67%) had a CA125 response of greater than 50%. Biomarker data will be presented as the trial data matures.

Conclusions: The combination of the AZD2014 and paclitaxel is tolerable in patients with HGSOC. This schedule has shown promising preliminary efficacy in a population of patients pre-treated with a paclitaxel-containing regimen.

Clinical trial identification: EudraCT#2012-003896-20

Legal entity responsible for the study: Institute of Cancer Research and Royal Marsden NHS Foundation Trust

Funding: EMC and AstraZeneca

Disclosure: All authors have declared no conflicts of interest.
Molecular imaging of Pgp/BCRP inhibition at the blood brain barrier using elacridar and [11C]erlotinib PET


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Background: Drug transporters such as Pgp and BCRP limit the exposure of several drugs to the brain. This study investigated the effect of the Pgp/BCRP inhibitor elacridar at the blood brain barrier of mice and cancer patients using the PET tracer [11C]erlotinib.

Methods: Elacridar (10, 25, 50 mg/kg) and cold erlotinib (20 mg/kg) were administered orally to wild type (WT) mice (n = 4 per group). Erlotinib was measured in blood and the brain ex vivo using LC-MS/MS. In addition, brain uptake was assessed using [11C]erlotinib (SA = 18.5 GBq/μmol, 10 μCi activity curves (TAC) and ex vivo scintillation counting in WT (n = 2) and Pgp/BCRP knockout (KO) mice (n = 2). No significant differences were found between WT and KO mice, both as TAC and as % of injected dose/g tissue (2.6-fold, p = 0.01). No significant differences were found between WT and KO mice, both as TAC and in vivo as % of injected dose/g tissue (2.6-fold, p = 0.01). In WT mice, erlotinib concentrations of ≥500 ng/mL resulted in increased brain concentration of erlotinib, achieving levels similar to KO mice, without affecting erlotinib plasma concentration. In patients, Vf of [11C]erlotinib did not increase after intake of elacridar (0.23 ± 0.11 versus 0.20 ± 0.07, mean ± SD, p = 0.43). [11C]OHT MET showed no significant changes in CBF. Excladric exposure in patients was 981 ± 192 ng/mL (mean ± SD).

Conclusions: When Pgp/BCRP was disabled in mice, brain uptake of erlotinib increased both at a tracer and pharmacological dose. In patients, brain uptake of [11C]erlotinib was not higher after administration of elacridar. The discrepancy between the preclinical and clinical results may be due to interspecies differences in abundance, activity and specificity of drug transporters in the mouse and human brain.

Clinical trial identification: Netherlands Trial Registry number: NTR7480 EUdraCT clinicaltrials database: 2014-000281-21

Legal entity responsible for the study: Netherlands Cancer Institute

Funding: Netherlands Cancer Institute

Disclosure: O. van Tellingen: Received research funding from Acon Pharmaceuticals (paid to institute). Co-inventor of patent US20140235631A1. A.A. Lammersma: Received research funding from Avad (paid to institute), received travel expenses and accommodation for a meeting co-sponsored by Philips. J.H. Steen: Owns stock in Medra Pharmaceuticals Holding, owns a patent on oral taxane formulations. N. Steeghs: Received research funding from Pfizer, GlaxoSmithKline, Novartis, Bayer, Boehinger Ingelheim and Roche. All other authors have declared no conflicts of interest.

Anti-tumor activity of PEGylated human IL-10 (AM0010) in renal cancer alone and in combination with anti-PD1


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Background: IL-10 is regarded as an immunosuppressive cytokine but it is also essential for the cytotoxicity and proliferation of antigen-activated CD8 T cells. Activation of the T cell receptor induces the expression of IL-10 receptors and PD-1 on CD8 T cells. This provides the mechanistic rationale for combining AM0010 and anti-PD1 for the treatment of cancer pts. Tolerability and anti-tumor activity of AM0010 alone and in combination with chemotherapy or immune checkpoint inhibitors was explored in a multi-basket phase 1 clinical trial.

Methods: Pts with advanced renal cell cancer (RCC) were treated with AM0010 alone (daily SC) or in combination with pembrolizumab (q4w IV). Tumor responses were monitored using RECIST. Immune responses were measured by analysis of serum cytokines, activation of blood derived T cells, peripheral T cell clonality.

Results: Nineteen pts. with RCC (15 evaluable), were treated with AM0010 alone (20 mg/kg) and eight were treated in combination with pembrolizumab (2mg/kg). Both regimens were well tolerated (observation period 15 mo for 1 drug). All TRAEs were transient and TRAEs leading to discontinuation were not observed. There was no colitis, pneumonitis, or endocrine disruptions. G3/4 TRAEs in monotherapy included anemia (9), hyperglycemia (3), thrombocytopenia (2), ALT/AST increase (2) and fatigue (2). AM0010 combination with pembrolizumab did not increase TRAEs. Objective responses (PR/CR) were observed in 4 of 15 evaluable RCC pts. in monotherapy (27%) and in 4 of 8 patients in AM0010 (50%). Progression free survival (PFS) was 3 and 9 months, respectively. AM0010 alone and in combination with anti-PD1 increased Th1 cytokines (IL-18, IFNγ, IL-7) as well as the number and proliferation of PD1+ activated CD8 T cells while decreasing the proliferation of FoxP3 + Tregs and TGFβ in the blood. AM0010 + anti-PD1 induced de novo oligoclonal expansion of T cell clones in the blood without affecting total lymphocyte counts.

Conclusions: AM0010 alone or in combination with anti-PD1 is well-tolerated. The clinical activity and the observed CD8 T cell activation encourages the continued exploration of AM0010 + anti-PD1.

Clinical trial identification: Clinicaltrials.gov NCT01009449

Legal entity responsible for the study: ARMO Bioscience - Martin OR

Funding: ARMO Biosciences

Disclosure: All authors have declared no conflicts of interest.
A phase I, open-label, multi-center, dose escalation study of oral NVP-CGM097, a p53/HDM2-protein-protein interaction inhibitor, in adult patients with selected advanced solid tumors

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Phase 53 is one of the most frequently inactivated proteins in human cancer, either through direct mutation of the TP53 gene or via suppressive mechanisms such as overexpression of HDM2. NVP-CGM097 is a potent and specific inhibitor of the HDM2/p53 interaction and has been shown to restore p53 function in preclinical models.

Methods: This is a multi-center, open-label Phase I, first in human study, enrolling patients (pts) with p53WT solid tumors. The primary objective is to determine the maximum tolerated dose (MTD), secondary objectives are to assess safety, tolerability, pharmacokinetics (PK), pharmacodynamics and preliminary antitumor activity. NVP-CGM097 was administered orally, initially in a continuous regimen three times weekly (3QW) in a 28-day cycle, and subsequently on an alternative regimen of 3QW in a two weeks on/one week off 21-day cycle. Dosing started at 10 mg SQW and escalation was guided by a Bayesian logistic regression model to determine the MTD. Peripheral blood was collected for PK at multiple time points during the first 24 hours and after multiple dosing, and plasma GDF-15 levels were assessed at pre- and post-treatment on day 1.

Results: 48 pts received at least one dose of NVP-CGM097. Post cycle 1 adverse event data suggested that the continuous regime (31 pts, dose range: 400-1000 mg, 2 pts ongoing) was not tolerated due to delayed grade 3/4 thrombocytopenia and/or neutropenia. The switch to the pre-defined alternative dosing regimen allowed escalation to higher doses (17 pts, dose range 500-1000 mg, 5 pts ongoing). Best overall responses were: 1 partial response (melanoma) 2.1%, 21 stable diseases (SD), 43.8%. Pts achieving SD had median duration of exposure of 24.14 weeks (wks) (range: 7.7-86.7 wks, ongoing pts censored at data cutoff date). 12 pts (25%) had duration of exposure of more than 24 wks. p53 pathway activation by NVP-CGM097 was demonstrated in pts by induction of its downstream target GDF-15 in serum and plasma.

Conclusions: NVP-CGM097 single agent shows clinical activity (disease control) in pts with solid tumors as demonstrated for pts who remained on study more than 24 wks. 7 pts (14.6%) are still on treatment and dose escalation is ongoing.

Clinical trial identification: NCT01790525 First received January 2, 2013
Legal entity responsible for the study: Novartis Pharma AG

Funding: Novartis Pharma AG

Disclosure: S. Bauer: Research support: Novartis, Blueprint Medicines, Ariad Consultant: GSK; Novartis, Pfizer, Bayer, Fresenius. Lilly, Blueprint Medicines Honoria (GMD): Pharmamar, GSK, Pfizer, Bayer Travel support: Pharmamar, Bayer. G. Demetri: The following interactions with NOVARTIS are noted as study support: 1. Consultant, consulting fees, 2. Patent on maitimid licensed to Novartis from Dana-Farber 3. Research support to Dana-Farber for clinical trial. S. Jeay: I am an employee and stockholder of Novartis A.G. R. Dummer: Research funding from Novartis, Merck Sharp & Dohme (MSD), Bristol-Myers Squibb (BMS), Roche, GlaxoSmithKline (GSK) and has a consultant or advisory board relationship with Novartis, MSD, BMS, Roche, GlaxoSmithKline, Amgen outside the submitted work. N. Guerreiro, E. Hallak: Novartis employee and stock owner. D.S. Tan: Consulting or advisory fees from Novartis, Bayer, Boehringer Ingelheim and Essai, honoraria from Novartis and Pfizer. research funding from Novartis, Bayer and GSK, and expense reimbursements from Novartis and MERCK, outside the submitted work. A. Kumar, C. Meille, L. Van Bree: Novartis employee. J.U. Wuertember: Employee of Novartis and has stock ownership of Novartis. P. Cassier: Received honoraria and research funding from Novartis, Roche, BluePrint and Amgen, as well as research funding from Eli Lilly, Celgene, AstraZeneca, GlaxoSmithKline, Merck Sharp Dohme, Merck Serono.

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Suppression of oncogene transcription - PNA as targeted cancer therapy for BRAF-V600E mutant melanoma


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Background: Our aim is to target tumor cells specifically by directly suppressing their oncogenes with peptide nucleic acid (PNA) oligonucleotides analogs. These bind to DNA over 1000-fold more avidly than its native complement and when conjugated to delivery peptides can be made nuclear and cell membrane permeable. We have employed these PNA oligomers to target BRAF V600E in a sequence-specific complementary manner in order to disrupt transcription.

Methods: For these studies, we have employed a novel delivery peptide conjugated to PNA modified to increase both cellular delivery and stability towards its target. We have assessed its ability to obstruct BRAF V600E transcription specifically in variety of cell lines by monitoring suppression of cell proliferation, BRAF V600E protein expression, and mRNA transcription. Tumor reduction was assessed through xenograft mouse models.
Results: Our results indicate that exposure of the melanoma cell lines to a modified PNA-peptide conjugate selective for BRAF V600E results in a concentration-dependent inhibition of cell growth that is specific for the BRAF V600E mutant melanoma cell lines with an IC50 range of 250 to 500 nM. Moreover, there is no inhibition of BRAF WT cell growth at these concentrations. This is associated with suppression of BRAF V600E protein over time. Furthermore, BRAF V600E protein expression was suppressed for up to 6 days following initial exposure proving its durability of inhibition. Exposure to this modified PNA-peptide down-regulated BRAF V600E mRNA transcription exclusively in the mutant cell lines. Live cell imaging of BRAF V600E mutant cells indicates localization of fluorescent-labeled PNA-delivery peptide conjugate to the nucleus within 3 hours of treatment. Xenograft mouse studies show reversal of tumor burden after four doses continuing for days following the last dose with a maximum tolerated dose to at least 50mg/kg.

Conclusions: Our results indicate that these PNA-peptide derivatives could represent a novel and promising new therapy for patients with BRAF V600E mutant melanoma and this technology could be applied to a multitude of other cancers either with specific translocations or mutations differing from wild-type cells even by only a single base pair.

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center

Funding: Memorial Sloan Kettering Cancer Center

Disclosure: All authors have declared no conflicts of interest.

Impact of tumor heregulin mRNA expression on outcome of patients with advanced/metastatic squamous NSCLC treated with lumretuzumab, a glycoengineered monoclonal antibody targeting HER3, in combination with erlotinib


Background: Preclinical data suggest that high mRNA expression levels of HER3 (HRG) are associated with anti-tumor activity of HER3-targeted therapy. In addition, preclinical data and clinical evidence from the phase 1 study of ODM-203, a novel and promising new therapy for patients with BRAF V600E mutant melanoma, and this technology could be applied to a multitude of other cancers either with specific translocations or mutations differing from wild-type cells even by only a single base pair.

Methods: Thirty-two patients (pts) with advanced or metastatic squamous NSCLC with specific translocations or mutations differing from wild-type cells even by only a single base pair.

Results: Median age was 66 years, pts had received a median of 2 prior lines of therapy, and 22% had previously received an FGFR inhibitor. In line with a previous report (Lassen et al., Ann Oncol 25; suppl. 4, iv147, 2014), diarrhea (78%) and rash (62%) were the most frequently reported adverse events. Overall, 2 pts (6%) achieved a confirmed PR with a duration of response of 3.8 and 4.9 months, respectively. The overall disease control rate (DCR) was 59% and median PFS was 2.0 months. In tumors expressing higher levels of HRG mRNA (n = 12), defined as expression levels above the median of an in-house squamous NSCLC tumor bank (n = 150 samples), ORR and DCR were 8% and 75%, respectively. PFS and duration of response were 2.9 and 3.8 months, respectively.

Conclusions: Lumretuzumab in combination with erlotinib demonstrated modest clinical efficacy in squamous NSCLC. Higher expression levels of HRG were associated with numerically higher rates of disease stabilization. However, ORR was low and duration of response and stable disease was relatively short, questioning the utility of tumor HRG mRNA as a clinically meaningful and robust biomarker for HER3 targeted therapy in squamous NSCLC.

Clinical trial identification: NCT01482377

Legal entity responsible for the study: Roche Pharma Research and Early Development

Funding: Roche Pharma Research and Early Development

Background: The c-Met receptor is overexpressed in multiple tumors. ABBV-399 is a first-in-class ADC composed of AET-700, a preclinical antibody conjugated to monomethyl auristatin E (a microtubule inhibitor). Preclinical data support ADC ABBV-399 as a unique strategy to deliver a potent cytotoxin directly to c-Met+ tumor cells (<30-50% of tumors overexpress c-Met).

Methods: In a 3+3 dose escalation design, ABBV-399 was administered at doses ranging from 0.15 to 3.3 mg/kg once every 21 days to pts with metastatic solid tumors (NCT02099058). ABBV-399 was then studied in a dose-expansion cohort in pts with c-Met+ (immunohistochemistry [IHC] H-score ≥150) non-small cell lung cancer (NSCLC). Overexpression of c-Met was assessed by an IHC assay utilizing the SP4 antibody (Ventana, Tucson, AZ, USA).

Results: As of March 31, 2016, 48 pts received at least 1 dose of ABBV-399. Among the 27 evaluable pts, a dose-dependent increase in target lesion response rates was observed. The most common grade ≥3 adverse events observed in more than 5% of pts included nausea (20.8%), neuropathy (14.6%), decreased appetite (12.5%), vomiting (12.5%), fatigue (10.0%), and pyrexia (6.7%).

Conclusions: ABBV-399 is well tolerated at a dose of 2.7 mg/kg every 21 days and has demonstrated promising antitumor activity in pts with c-Met+ NSCLC. Assessment of antitumor activity and safety of ABBV-399 in c-Met+ pts will continue as a phase II study.

Clinical trial identification: NCT02099058

Legal entity responsible for the study: AbbVie, Inc.

Funding: AbbVie, Inc.


First-in-human phase 1, dose-escalation and -expansion study of ABBV-399, an antibody-drug conjugate (ADC) targeting c-Met, in patients (pts) with advanced solid tumors


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A phase Ib study of lumretuzumab, a glycoengineered monoclonal antibody targeting HER3, in combination with carboplatin and paclitaxel as first-line treatment in patients with squamous non-small cell lung cancer


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Background: Preclinical data suggest that high mRNA expression levels of hengulin (HRG) could predict anti-tumor activity of lumretuzumab, an anti-HER3 antibody.

HRG mRNA is more highly expressed in squamous (sq)NSCLC compared to non-sqNSCLC.

Methods: This was an open-label, multicenter phase Ib study in patients (pts) with advanced or metastatic sqNSCLC who have not received prior chemotherapy or targeted therapy for NSCLC. Lumretuzumab (880 mg) was administered in combination with carboplatin (AUC 6 mg/mL x min) and paclitaxel (200 mg/m²) on a q3w schedule. The primary objectives were to evaluate safety and efficacy and an exploratory objective was to correlate tumor HRG mRNA expression to clinical activity.

Results: ABBV-399 gene expression levels were assessed by RT-PCR in archival formalin-fixed paraffin-embedded tumor samples. To distinguish high vs low HRG gene expression levels, the median gene expression level of sqNSCLC tumor samples from an internal tumor bank (n = 150) was used as an exploratory cut-off. Twelve pts were enrolled (median age 66.5 years, 10 pts male). The most frequently reported adverse events (AEs) (≥32 pts) were diarrhea (9 pts), asthenia (8 pts), neutropenia (5 pts), nausea and anemia-related related (4 pts each). Grade 3 AEs were only reported for single pts except for anemia which was reported for two pts. Overall, three pts achieved a partial response (25%) and 8 pts achieved stable disease (67%). High HRG mRNA expression levels were found in 7 pts (58%). All three responding pts showed high HRG mRNA expression levels. The duration of responses was 2.8, 6.0, and 6.2 months.

Conclusions: Lumretuzumab in combination with carboplatin and paclitaxel was safe and well tolerated. While all 3 responding pts had tumors with high HRG mRNA expression levels, the addition of lumretuzumab to platinum-based therapy was not associated with a clear signal of higher clinical activity than what would have been expected with platinum-based therapy alone.

Clinical trial identification: NCT02201435 First received: July 24, 2014 |

Legal entity responsible for the study: Fa. Hoffmann-La Roche

Funding: Fa. Hoffmann-La Roche

Disclosure: E. Felip: Consulting fees from: Eli Lilly, Pfizer, Roche, Boehringer Ingelheim, MSD Lecture fees from: Astra Zeneca, BMS, Novartis. C. Adessi, F. Michieli, J. James, M. Ceppi, M. Weiss, Sponsor employee. W. Jacob: Sponsor employee Support owner. A. Cervantes: Consulting fees from: Merck Serono, Agen, Servier, Roche, Lilly, Novartis Research support from: Merck Serono, Agen, Servier, Lilly, Novartis, MSD, Roche, Genentech. All other authors have declared no conflicts of interest.

A phase II study of apatinib, a highly selective inhibitor of VEGFR-2, in patients with metastatic solid tumors without standard treatment options


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Background: VEGFR-2 signaling has a pivotal role in tumor angiogenesis. Apatinib (YN906D1) is a highly selective tyrosine kinase inhibitor of VEGFR-2. A previous phase I study of continuous daily dosing of apatinib in solid tumors identified 850 mg per day as the recommended dose (Sharma et al., 2015 ASCO). This study was a phase II trial evaluating the preliminary efficacy and safety of apatinib in advanced solid tumors.

Methods: In Korea and the US, 30 patients (pts) with metastatic GC (n = 15), CRC (n = 9), NSCLC (n = 3), NET (n = 2) or mesotheloma (n = 1) who failed standard chemotherapy received apatinib 850 mg p.o. q.d. until disease progression or unacceptable toxicity. Other key eligibility criteria included presence of measurable lesions and an ECOG performance status ≤2.

Results: Among the 30 pts, 21 pts (70%) were male, and the median age was 56.5 years (range, 32–82). Twenty-three pts (76.7%) were Asian, and the remaining 7 pts (23.3%) were Caucasian. In 28 evaluable pts, partial response (PR) was noted in 3 pts (10.7%, 1 GC, 1 NSCLC, and 1 NET), and stable disease (SD) in 23 pts (82.1%) with a disease control rate (DCR) of 92.9% at 8 weeks. All 15 GC pts received with 1 PR (6.7%), 12 SD (80.0%), and 2 cases of progressive disease (PD) (13.3%), resulting in a DCR of 86.7%. Grade ≥3 adverse events observed in more than 5% of pts included hypertension (n = 7), increased blood bilirubin (n = 4), hypokalemia (n = 3) and hand-foot skin reaction (HSFR) (n = 2). Toxicities were generally well tolerated, and there was no toxicity-related death.

Conclusions: Apatinib showed a promising anti-tumor activity in advanced solid tumors after failure of standard treatment, and was well tolerated with manageable toxicity profiles. The results of this study support further investigation of apatinib in solid tumors, especially in gastric cancer in which efficacy and safety of apatinib has been reported in a Chinese phase I study.

Clinical trial identification: NCT01497704

Legal entity responsible for the study: LSK BioPharma, Bukwang Pharm. Co. Ltd

Funding: LSK BioPharma, Bukwang Pharm. Co. Ltd
Phase I dose escalation (esc) trial of weekly intravenous (i.v.) BI 836845 in Japanese patients (pts) with advanced solid tumors

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Background: BI 836845 is an insulin-like growth factor (IGF) ligand-neutralizing humanized antibody that binds to IGF-1/IGF-2 ligands. This Phase I trial (NCT02145741) evaluated the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), pharmacodynamics (PD), and activity of BI 836845.

Methods: Japanese pts with advanced solid tumors were recruited in a 3 + 3 dose escalation design. BI 836845 was administered weekly i.v. (21-day cycles). Pts with IGF-driven tumors were recruited in an expansion (exp) cohort.

Results: In the esc part, 15 pts (60% male; median age 67 years, range 47–74), 64–76, Eastern Cooperative Oncology Group performance status 0/1 (67/33% of pts) received BI 836845 across 3 doses: 750 mg (n = 6), 1000 mg (n = 3), and 1400 mg (n = 6). Tumor types included esophageal (3), stomach (3), adrenal (2), colorectal (2), and non-small cell lung (2). No dose-limiting toxicities were observed, MTD was not reached. A relevant biological dose was selected at 1000 mg weekly i.v. based on previous safety, efficacy, and PK/PD data. In the exp part, 6 pts (median age 38 years, range 32–71) received BI 836845 across 1000 mg (n = 3) and 1400 mg (n = 2). Tumor types included esophageal (2) and colorectal (1). In total, 12/21 (57%) pts had drug-related adverse events (AEs); of those ≥20% pts were fatigue (19%), neutropenia (19%), diarrhea (14%) and white blood cell count decreased (14%). No pt had a dose reduction or discontinued due to AEs. No relevant deviations from dose linearity of BI 836845 exposure were observed in the PK analysis (esc part). 515 pts (33%) in the esc part had stable disease (SD, mean duration 95 days). In the exp part, 1/6 (17%) pts at 1400 mg SD had a partial response and 2/6 (33%) SD had SD (disease control rate 50%, mean duration 102 days).

Conclusions: These findings were similar to those of previous Phase I studies of weekly i.v. BI 836485 in Caucasian or other Asian patients.

Clinical trial identification: Clinical trial registration: NCT02145741

Legal entity responsible for the study: Boehringer Ingelheim

Disclosure: T. Doi: Membership on advisory board or board of directors (Boehringer Ingelheim); corporate sponsored research (Boehringer Ingelheim); T. Kojima: Research funding (Merck Serono). T. Yoshino: Corporate-sponsored research (GlaxoSmithKline, Boehringer Ingelheim); employment (Boehringer Ingelheim). T. Bogenrieder: Employment (Boehringer Ingelheim).

All other authors have declared no conflicts of interest.
three of these studies and standard genotyping methods. Associations with PK were evaluated using linear regression.

**Results:** Compared with Western subjects, dose-normalised AUC and Cmax were 35% and 39% higher respectively in Asian subjects, adjusting for baseline bodyweight (Table 1). Exposure was similar among Western subjects. Geomeans for dose-normalised AUC and Cmax ranged from 2% to 18% greater for NJA and IND compared with JP, indicating exposures are similar across Asian populations. Genetic analysis showed that allele frequencies of variants in CYP2C19, UGT1A1 and ABCG2 varied between ethnic groups. The genetic variants CYP2C19*2, CYP2C19*3, CYP2C19*17, UGT1A1*6, UGT1A1*26, and ABCG2 421C > A, did not show any clear associations with selumetinib exposure after correction for multiple testing.

**Conclusions:** Selumetinib exposure was greater in Asian than Western subjects. Although allele frequencies differed between populations, there did not appear to be any associations between the genetic variants analysed and selumetinib exposure. Data provide valuable insight for the use of selumetinib in Asian populations.

**Clinical trial identification:** NCT01635023, NCT01974349, NCT02056392, NCT02232749, NCT02238782, NCT02063204, NCT02063230, NCT02093728, NCT02046850, NCT01960374.

**Legal entity responsible for the study:** AstraZeneca

**Funding:** AstraZeneca


**References:**


**Background:** The mTOR signaling pathway is frequently dysregulated in human cancers. TAK-228 is an investigational, orally available, highly selective mTOR inhibitor. Larger scale manufacturing of TAK-228 required a formulation change from unmilled to milled drug substance. Here we present safety, tolerability, and preliminary efficacy, as well as pharmacokinetics (PK) under fed and fasted conditions, of milled TAK-228.

**Methods:** Escalation cohorts of eligible pts (aged ≥ 18 y with advanced non-hematologic malignancies) were concurrently enrolled into 3 arms: once daily (QD), once weekly (QW), and three days each week plus weekly paclitaxel 80 mg/m² (QDx3QW + P). Starting doses of milled TAK-228 were 4 mg QD, 20 mg QW and 6 mg QDx3QW + P, representing a one-dose-level reduction compared to the previously established recommended phase 2 doses of unmilled TAK-228. The effect of food on milled TAK-228 was assessed in a 2-period, randomised, cross-over study with 72 evaluable pts.

**Results:** The mTORC1/2 inhibitor TAK-228 (MLN0128) was well tolerated in patients (pts) with advanced solid tumors. Three mTORC1/2 hits were identified: a S477R (41%), S2485R (11%), and S1228T (11%) mutations. Tumors with mTORC1/2 hits showed increased phosphorylation of downstream targets, suggesting TAK-228 as a novel therapy for these tumors. In vitro studies showed a selective inhibitory effect on proliferation and viability of tumor cells. TAK-228 showed a dose-dependent inhibition of cell proliferation in tumor cell lines expressing mTORC1/2 hits. TAK-228 demonstrated promising efficacy in a phase 2 trial in patients with advanced solid tumors. The recommended phase 2 dose was 6 mg QDx3QW + P.

**Conclusion:** TAK-228 is a promising mTORC1/2 inhibitor with potential for clinical development in patients with advanced solid tumors.
TAK-228 PK was evaluated in 14 of 16 pts in the QD arm enrolled into a designated PK run-in cohort; the PK of milled TAK-228 was assessed in all pts. Results: At data cut-off (March 11, 2016), 61 pts (median age 64 y [28–88]) were enrolled and formed the safety-population, n = 58 the response-population, and n = 53 the PK-population. The safety and preliminary efficacy results are presented (Table) Preliminary PK comparisons of 4 mg milled TAK-228 QD under fed (n = 14) and fasted (n = 13) conditions reported a clinically meaningful 38% reduction in Cmax and a delay in absorption with food (median T1/2 6 h [fed] vs 2 h [fasted]), with no meaningful change in total AUC. Conclusions: Safety was established for milled TAK-228 at the MTDs of 3 mg QD, 30 mg QW and 6 mg QDx3QW + P, lower doses than the MTDs identified for unmilled TAK-228. PK data suggest that a relevant food effect might be attributable for the observed difference in tolerability. Preliminary efficacy seen with milled TAK-228 is encouraging.


Determination of recommended phase II dose of ABTL0812, a novel regulator of Akt/mTOR axis, by pharmacokinetic-pharmacodynamic modelling

J. Alfon1, L. Vidal2, L. Gabin1, I. Victoria3, M. Gis3, B. Laguerre3, M. Brunet2, H. Cisarò1, J. Pizarro10, I. Corta3, M. Gonnez-Ferriera1, P. Muñoz1, G. Falcho1, T. Eraso6, P. Gascon2

Background: ABTL0812 is an antiangiogen in clinical development with a novel mechanism of action. It inhibits the Akt/mTOR axis after binding to PPARs and subsequent induction of TBID3, a pseudokinase that acts as a negative regulator of Akt. Preclinical studies have shown high efficacy in different tumor types including NSCLC, endometrial cancer, pancreatic cancer and neuroblastoma. ABTL0812 exhibits efficacy in resistant models and synergy with chemotherapy while maintaining extremely low toxicity.

Methods: A phase Ib clinical trial with a 3 + 3 dose expansion and an design expansion was performed in patients with advanced solid tumors. Safety and tolerability were the main objectives of the trial. ABTL0812 pharmacokinetics (PK) was determined and the ratio between phosphorylated Akt and total Akt (pAkt/Akt) levels in platelets was used as pharmacodynamic (PD) biomarker. Preliminary antitumor activity was evaluated by RECIST 1.1 criteria.

Results: In the dose-escalation phase, 15 patients received 500 mg qd, 1000 mg qd, 1800 mg bid and 2000 mg bid. Other 14 patients were included in the expansion part at a dose of 1300 mg tid. No dose-limiting toxicities were detected. Most AEs were grade 1-2, and only one patient had drug-related grade 3-4 AEs. Several long-term disease stabilizations were observed, including one patient with cholangiocarcinoma (>268 weeks), one with endometrial cancer (60 weeks) and three with colorectal cancer (22-28 weeks). Linear pharmacokinetics was described after multiple daily dosing, as well as dose-dependent inhibition of pAkt/Akt. A PK/PD Inhibitory Effect model was performed and it was found that at least bid administration was required to have sustained inhibition of the biomarker >50%. In addition, it was shown that 1300 mg tid achieved pAkt/Akt inhibition in the range 74.7-95.5%, confirming that this dose induced the highest inhibition of the pathway.

Conclusions: Phase Ib clinical trial results have shown a high safety profile and signs of efficacy. PK has been described and concentration-dependent inhibition of a surrogate biomarker has been demonstrated. RP2D was established at 1300 mg tid based on a PK/PD analysis using the ratio of pAkt/Akt in platelets as a surrogate biomarker.

Clinical trial identification: Eudra CT 2013-001293-17; Clinicaltrial.gov NCT02201823


Annals of Oncology
Background: NVP-CGM097 is a select p53-HDM2 protein-protein interaction inhibitor currently in Phase I clinical development for the treatment of patients with p53 wild type malignancies. Delayed thrombocytopenia is the primary dose limiting toxicity reported upon NVP-CGM097 treatment. Anticipation of the onset and severity of thrombocytopenia is critical for improved patient outcome. The aim of this work was to develop mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) models to provide an integrated quantitative understanding of safety and efficacy profiles.

Methods: Population PK, PK/PD models of thrombocytopenia and the cytokine Growth Differentiation Factor 15 (GDF-15, as a marker for p53 pathway activation), and a kinetic (K)/PD model of tumor size was developed based on data from 48 solid tumor patients collected from the first-in-human Phase I study (NCT01760525) conducted with orally administered NVP-CGM097.

Results: The PK/PD model for thrombocytopenia was derived from Friberg et al. (2002) with an additional feedback mechanism and implementation of platelet (PLT) transfusion events. The model accurately reproduced the PLT time course after NVP-CGM097 administration, as well as the impact of drug on GDF-15 levels. An association between individual model-estimated drug potency on PLTs and drug potency on plasma GDF-15 levels was investigated as a descriptor of PLT change in addition to drug exposure, raising the possibility of using GDF-15 induction as a prospective marker for delayed thrombocytopenia. A kinetic (K)/PD efficacy model was also developed for the same patient population to describe tumor size as a function of dose. Large variability was seen in the tumor growth parameter while moderate variability was observed for drug potency on tumor size.

Conclusions: This work further supports the use of such approaches for the clinical development of HDLM2 inhibitors, and explores the feasibility of utilizing these as a rational approach for titrating regimens and doses for individual patients at risk for thrombocytopenia while maximizing patient benefit. References 1. Friberg LE, et al. J Clin Oncol 2002;20:4713–4721.

Legal entity responsible for the study: Novartis Pharma AG

Funding: Novartis Pharma AG


Legal entity responsible for the study: GSK

Funding: GSK

Disclosure: J. Infante: Research funding from GSK, R. Govindan, D. McMahon personal fees from Boehringer Ingelheim, GlaxoSmithKline, Cegene, Merck, Bayer, Genentech, Clovis Oncology, Helsinn Healthcare and Pancreatin outside the submitted work. A. Dhar: Full-time/part-time employee of GSK. Stock shareholder (self managed) of GSK. All other authors have declared no conflicts of interest.
Results: In vitro, inhibition of DNA-PK by VX-984 had potent cytotoxic activity in combination with doxorubicin and etoposide in established cancer cell lines and in primary tumor explants from ovarian and endometrial cancers (doxorubicin) and small cell lung cancer (etoposide). Bliss synergy scores of ≥23% (strong synergy) were observed for doxorubicin and etoposide in the presence of VX-984. Further, the activity observed with VX-984 was associated with enhanced DNA damage as measured by phosphorylated Kruedel-associated protein (pKAP1) and phosphorylated histone H2AX (gamma-H2AX), consistent with full DSB repair. In vivo, VX-984 significantly enhanced the efficacy of pegylated liposomal doxorubicin (PLD) in an ovarian cancer patient-derived xenograft model as well as in cancer cell line xenograft models.

Conclusions: These data provide evidence that inhibition of DNA-PK by VX-984 enhances the efficacy of DSB-inducing agents in preclinical models and support the use of VX-984 in combination with agents such as PLD for the treatment of ovarian and endometrial cancers. VX-984 is currently in a Phase 1 clinical trial in combination with PLD.

Legal entity responsible for the study: Vertex Pharmaceuticals Incorporated

Funding: Vertex Pharmaceuticals Incorporated


**RAS/AKT pathway mutations as predictive biomarkers in patients with colorectal cancer treated with the export 1 (XPO1) inhibitor selenosin (SEL) – inhibition of nuclear- cytoplasmic translocation of p27 as a mechanism of anti-tumour activity**

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Background: Localization of p27 within a cell determines its function. Cytoplasmic sequestration of p27 promotes oncogenic activity while its nuclear retention inhibits tumorigenesis. RAS activation in tumours indirectly causes cytoplasmic sequestration of p27 via the activation of its effectors PI3K/AKT and Raf/MEK/ERK pathway. SEL is a potent XPO1 inhibitor that forces nuclear retention of multiple proteins including p27 through inhibition of the PI3K/AKT and Raf/MEK/ERK pathway.

Methods: SEL was administered orally to patients with advanced solid cancers in a phase 1 dose escalation study. Response was evaluated every two cycles (RECIST v1.1). Nuclear-cytoplasmic localisation of p27 in p27 RAS and/or AKT activated tumours from tumour biopsies before and post SEL were determined together with nuclear retention of other XPO1 cargo proteins, proliferative and apoptotic markers.

Results: Of 18 advanced colorectal cancer (CRC) patients known with RAS and AKT pathway mutational status (12/16/6; median age 59.5; ECOG PS 0/1: 9/9), who reached 8 weeks of SEL were analysed. 50% (n = 9) had an activating mutation in the RAS pathway (KRAS/NRAS/BRAP: 7/15/1; 16.7% (n = 4) in the AKT/PI3K pathway (PIK3/AKT/PTEN loss: 1/1/1); 11.1% (n = 2) in both and 44.4% (n = 8) did not harbour mutations in either (WT). Median PFS for patients with a mutation in either pathway compared to WT patients were 78 days vs 50 days, respectively; (p = 0.001). Patients with a mutation in the RAS pathway (KRAS/NRAS/BRAF: 7/1/1; 11.1% in both and 44.4% in the PI3K/AKT pathway (PIK3/AKT/PTEN loss: 1/1/1); 11.1% (n = 2) in both and 44.4% (n = 8) did not harbour mutations in either (WT). Median PFS for patients with a mutation in either pathway compared to WT patients were 78 days vs 50 days, respectively; (p = 0.001).

Conclusions: RAS and AKT pathway activated CRC appear to have a longer PFS with an increased number of patients achieving DCR of >3 months compared to WT tumours. Cytoplasmic translocation of p27 could be a key oncogenic mechanism in RAS and/or AKT pathway activated tumours and can be targeted by inhibition of XPO1.

Legal entity responsible for the study: National University Hospital, Singapore

Funding: Study support: Karyopharm Therapeutics Inc. and National Medical Research Council

Disclosure: D. Tan: Advisory board - Astra Zeneca. All other authors have declared no conflicts of interest.

**Phase 1/2a study of RX-5902 in advanced solid tumors (ST): An orally bioavailable inhibitor of phosphorylated P68 and modulator of β-catenin nuclear translocation**

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Background: RX-5902 is a novel compound targeting phosphorylated p68 (p-p68) RNA helicase (ie, DDX5), a member of the DEAD box family of RNA helicases. p-p68 may play a role in cell proliferation and cancer progression by blocking the nuclear translocation of β-catenin. Final data from the first clinical study of single agent RX-5902 to treat solid tumors and the ongoing Phase 2a in advanced triple-negative breast cancer (TNBC) and ovarian cancer (OC) are described.

Methods: This is a Phase 1/2a study (NCT02030092) designed to evaluate safety, tolerability and pharmacokinetics (PK) following increasing doses of RX-5902 at varying schedules. Primary objectives include safety, tolerability and dose limiting toxicities to identify the maximum tolerated dose and a recommended phase 2 dose and schedule (RP2D). Secondary objectives were PK and antitumor activity. Eligible subjects (aged ≥18 years) with relapsed/refractory ST received oral RX-5902 at 1, 3, 5 or 7 mg per week for 3 weeks followed by 1 week of rest or for 4 weeks. Based on the RP2D of the Phase 1, a Phase 2a is ongoing in patients with advanced TNBC and OC in a 2-stage design.
**Results:** As of May 2016, 24 subjects were enrolled (11 Females, 13 males). No dose limiting toxicities or treatment related SAEs were reported. Seven subjects experienced stable disease (breast, neuroendocrine, paraganglioma, squamous cell cervical and colorectal cancers); 3 subjects received treatment for > 1 year. The most common side effects were grade 1 related adverse events nausea, vomiting and fatigue; no grade 2 related events were reported. RX-5902 was orally bioavailable with median Tmax of 2 hours and half-life of 12 hours. Doses were successfully escalated to 300 mgs daily for 5 days, with a week on, 1 week off schedule. Daily doses of 300-400 mgs daily for 28 days are being tested.

**Conclusions:** RX-5902 is safe and well tolerated at the doses and schedules tested. A early anti-tumor activity was observed in patients with breast, neuroendocrine, paraganglioma, squamous cell cervical and colorectal cancers. Final results from the phase 1 and data on the first stage of the Phase 2a in patients with TNBC and advanced OC will be presented.

**Clinical trial identification:** NCT02003092

**Legal entity responsible for the study:** Rexahn Pharmaceuticals, Inc.

**Funding:** Rexahn Pharmaceuticals, Inc.

**Disclosure:** C. Petersen, R. Mazhari, E. Benaim: Employee of Rexahn Pharmaceuticals, Inc. All other authors have declared no conflicts of interest.

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**Background:** TP53 mutations are ubiquitous in HGOC. APR-246 stabilizes mutant p53 and drives it to a conformation and through its active moiety MQ, also depletes glutathione and inhibits thiorodoxin reductase. These mechanisms of action potentiate chemosensitivity of cancer cells. This study aimed to establish the recommended phase II dose (RPTD) of APR-246 in combination with C and PLD.

**Methods:** A 3 + 3 dose escalation study of APR-246 (35, 50 and 67.5mg/kg IV on days 1-4) in combination with C AUC5 and PLD 30mg/m2 given on day 4 in 28-day schedule. Eligible patients had platinum sensitive relapsed HGOC with archival tumour specimens demonstrating cyttoplasmic mutant p53 staining. Following recruitment to the three dose cohorts (3 + 6 + 6) further patients were included in dose level (DL) 1 and DL2 cohorts to evaluate possible dose dependency of safety and efficacy. CA-125 was tested at each cycle, and CT scans performed every two cycles.

**Results:** All 3 dose escalation cohorts have completed recruitment with expansion of DL2 (due to one dose limiting toxicity (DLT) of ruptured diverticulum) and DL3 (RPTD). No dose dependent signals in activity or toxicity were established. The main toxicity attributable to APR-246 was dizziness in 20 out of 28 patients (71%; 18 grade 1, 2 grade 2, 2 grade 3). There were no pharmacokinetic interactions between APR-246 and C/PLD. To date, of 17 patients evaluable for CA125 response (GCIG Intergroup criteria) with OC with partial response had platinum resistance relapses observed in 8 (17%): 8 PRs (NSCLC: 2/30 pts, 6.7%; OC: 6/16 pts, 37.5%). Most pts with OC with partial response had platinum resistance relapses.

**Conclusions:** On successfully completing the trial, the recommended dose of APR-246 in combination with C Carbo (AUC5) and Carbo (75 mg/m2) on Day 7 and 14 and Cis (75 mg/m2) on Day 7 of each cycle for 1st arm NSCLC pts received Q with G (1000 mg/m2) on Days 7 and 14 and Cis (75 mg/m2) on Day 7 of each cycle for first line NSCLC. In the 2nd arm pts received Q with P (175 mg/m2) and Carbo (AUC5) on Day 7 of each cycle, in 2nd or subsequent lines for pts with NSCLC or OC. Dose escalation was according to the 3+3 dose-limiting toxicity (DLT) algorithm. After definition of MTD, additional pts were to have been included.

**Results:** 51 pts (QGCis – 28 pts, QPCarbo – 23 pts, NSCLC – 33 pts, OC – 18 pts) were enrolled. 49% male; median age = 56 (range 47-74) years. There were no DLTs. Q was tolerated to the maximum dose of 12 mg chosen for this study, and therefore there were MTD criteria never met. Q at 12 mg in combo was chosen and is dose recommended for Phase 2 development. The most common adverse events (AE) were neutropenia - 56% and 57%, thrombocytopenia - 39% and 75%, anemia - 35% and 64% for group of QPCarbo and QGCis, respectively. Any serious AE were revealed in 21.6% pts, Q related serious AE - in 13.7%, AE grade – in 64.7%, and 23.5% pts discontinued therapy due to AE. 46 pts were evaluable for response, with responses observed in 18% (7): 8 PRs (NSCLC: 230 pts, 67.6%, OC: 6/16 pts, 37.5%). Most pts with OC with partial response had platinum resistance relapses.

**Conclusions:** One successfully completing the trial, the recommended dose of Q for phase 2 study is 12 mg in combination with C G(1250 mg/m2) and Cis (75 mg/m2) or P (175 mg/m2) and Carbo (AUC5). The combination QPCarbo showed activity in the treatment of pts with platinum resistant OC.

**Clinical trial identification:** NCT02728492

**Legal entity responsible for the study:** N/A

**Funding:** NewVac


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**Background:** The mechanism of action of quisinostat (Q) includes protein acetylation, leading to re-activation of tumor suppressor genes and restoration of tumor sensitivity to chemotherapy.

**Methods:** The primary endpoint was to identify the maximum tolerated dose (MTD) of Q. Secondary endpoints included safety, overall response rate, and pharmacokinetics parameters. Q was administered orally at escalated doses (8, 10 and 12 mg), 3 week cycle on Days 1, 3, 5, 7, 9, 11. In the 1st arm NSCLC pts received Q with G (1000 mg/m2) on Day 7 and 14 and Cis (75 mg/m2) on Day 7 of each cycle, for 2nd line. If Q was dose limiting tolerable at 12 mg, another dosage cohort was to have been started. Q at 12 mg with G (1250 mg/m2) on Days 7 and 14 and Cis (75 mg/m2) on Day 7 of each cycle for 1st line NSCLC. In the 2nd arm pts received Q with P (175 mg/m2) and Carbo (AUC5) on Day 7 of each cycle, in 2nd or subsequent lines for pts with NSCLC or OC. Dose escalation was according to the 3+3 dose-limiting toxicity (DLT) algorithm. After definition of MTD, additional pts were to have been included.

**Results:** 33 pts, OC (31 patients (QGCis – 28 pts, QPCarbo – 23 pts, NSCLC – 33 pts, OC – 18 pts) were enrolled. 49% male; median age = 56 (range 47-74) years. There were no DLTs. Q was tolerated to the maximum dose of 12 mg chosen for this study, and therefore there were MTD criteria never met. Q at 12 mg in combo was chosen and is dose recommended for Phase 2 development. The most common adverse events (AE) were neutropenia - 56% and 57%, thrombocytopenia - 39% and 75%, anemia - 35% and 64% for group of QPCarbo and QGCis, respectively. Any serious AE were revealed in 21.6% pts, Q related serious AE - in 13.7%, AE grade – in 64.7%, and 23.5% pts discontinued therapy due to AE. 46 pts were evaluable for response, with responses observed in 18% (7): 8 PRs (NSCLC: 230 pts, 67.6%, OC: 6/16 pts, 37.5%). Most pts with OC with partial response had platinum resistance relapses.

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**Clinical trial identification:** NCT02728492

**Legal entity responsible for the study:** N/A

**Funding:** NewVac

**Clinical trial identification:** NCT02280317

**Legal entity responsible for the study:** N/A

**Funding:** Valitx, Inc

**Disclosure:** A. Boyd: Is employed as a Consultant by Valitx as a medical monitor for the trial. G. Morris: Employee of Valitx. All other authors have declared no conflicts of interest.

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**Background:** Adenosine is immunosuppressive and is produced at high concentrations in tumors by both CD73 and direct release from tumor cells. Adenosine activates A2AR, an immune checkpoint that leads to direct suppression of effector T cells and stimulation of regulatory T cells. CPI-444 is an oral, selective A2AR inhibitor that has shown promise in preclinical models and reflects effector T cell activation, similar to reports by others in PD-1+ CD8+ cells (1.7 and 2.4 fold compared to baseline). This is consistent with immunohistochemistry and gene expression.

**Methods:** An accelerated titration, open label, dose-escalating design has been used to identify a maximum tolerated/administered dose (MTD/MAD). VAL-201 is given subcutaneously on Days 1, 5, and 8. The starting dose was 0.5 mg/kg. Expansion to a 3+3 design was planned to occur at dose level (DL) 3. Dose limiting toxicity (DLT) was assessed during Cycle 1 and safety evaluations were conducted weekly.

**Results:** Eight patients have been recruited to 4 DLA (0.5 mg/kg n = 1; 1.0 mg/kg n = 1; 2.0 mg/kg n = 3; 4.0 mg/kg n = 3). Patient demographics are in Table 1. The final planned escalation will be 5.0 mg/kg, the maximum feasible single dose which may be administered or tolerated. The only drug-related adverse event (AE) observed has been Grade 1 injection site reaction. Median duration on trial is currently 85 days. Early signs of clinical activity have been observed with prolonged PSA doubling time (n = 2), stabilization of PSA (n = 1) and >50% decrease in PSA (n = 1, Table).

**Conclusions:** VAL-201 is well-tolerated with early signs of clinical activity in advanced prostate cancer. No DLT has been observed. The MTD/MAD has not yet been identified and the study continues. Expansion to other tumor types is planned. PK data analysis is ongoing and will be presented.

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**Background:** Evaluation of patient's life expectancy is crucial to select patient who may benefit from phase I studies. The Royal Marsden Hospital score (RMH) established a prognostic tool validated in prospective studies and based on 3 objective variables: number of metastatic sites, LDH and serum albumin. Nevertheless, it remains unclear if those factors could be extended to immunotherapy phase I trials.

**Methods:** A retrospective analysis of risk factors of early death for patients enrolled into immune checkpoint inhibitor phase I trials in our institution was conducted. Demographic and biological characteristics (age, gender, number of metastatic site, LDH, albumin, neutrophil-to-lymphocyte ratio, hemoglobin, platelet count) were analyzed with univariate and multivariable analysis for overall survival.

**Results:** 155 patients (Male: 83, Median age was 59 (22-90)) treated with an experimental immunotherapy between March 2012 and January 2016 were analyzed. The most frequent tumor types were non-small cell lung cancer (16.7%), head and neck cancer (12.2%), urothelial cancer (10.3%), renal cancer (9%), breast cancer (7.7%); the most frequent tumor types were non-small cell lung cancer (16.7%), head and neck cancer (12.2%), urothelial cancer (10.3%), renal cancer (9%), breast cancer (7.7%); the most frequent tumor types were non-small cell lung cancer (16.7%), head and neck cancer (12.2%), urothelial cancer (10.3%), renal cancer (9%), breast cancer (7.7%)

**Conclusions:** CPI-444 is well-tolerated and demonstrates biological activity indicating activation of T cell immunity. This may be an immunotherapy phase I trials.

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**Background:** Clinical trials involving immunotherapy in advanced cancers have been conducted in the past two decades. Clinical data have shown that combining PD-1 inhibitors with other immunotherapies, such as vaccination, can lead to improved outcomes. However, the role of adenosine in these combinations remains unclear. CPI-444, an oral, selective A2AR inhibitor, is being studied in an ongoing Ph1b trial in solid tumor patients.

**Methods:** We conducted a preclinical and clinical study to evaluate the Biomarker and clinical activity of CPI-444, a novel small molecule inhibitor of A2A receptor (A2AR), in a Ph1b study in advanced cancers.

**Results:** CPI-444 was well-tolerated and the minimum of three months dose escalation of 4.0 mg/kg was administered. No DLT has occurred to date. The only drug-related adverse event (AE) observed has been Grade 1 injection site reaction. Median duration on trial is currently 85 days. Early signs of clinical activity have been observed with prolonged PSA doubling time (n = 2), stabilization of PSA (n = 1) and >50% decrease in PSA (n = 1, Table).

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Lurbinitectin (PM01183) plus paclitaxel (P), recommended dose (RD) expansion results with or without the addition of bevacizumab (Bev) in patients (pts) with selected solid tumors


Background: The recommended ID of PM01183 + P is PM01183 2.2 mg/m² on Day (D) 1 + P 80 mg/m² D1&8 q3w. We provide updated results after RD expansion (A), and after Bev 15 mg/kg addition on D1 (B).

Methods: RECIST v1.1 evaluable pts ≤ 75 yrs (y) old, with EOCOG PS ≤ 1, adequate organ function and ≤ 3 prior advanced lines were eligible. Prior taxanes were allowed if last dosed ≥ 3 months prior; prior weekly P or NAB-P were excluded. P was discontinued after 18 weeks and pts continued on PM01183 alone (A) or plus Bev (B). Pharmacokinetics (PK) was assessed in C1.

Results: As of April 2016, 37/12 pts were treated (cohort A/B, accordingly); 2/37 and 3/10 pts had DLT in Cycle 1; 33/37 and 3/10 pts had DLT at RD. Durable responses occurred in half of MBC pts. No G4 hematological toxicity or G3 fatigue or hypertension occurred once. G1/2 toxicities in ≥ 10% of pts were: nausea, diarrhea, vomiting, fatigue, mucositis and HFS. Efficacy: 12/25 MBC pts responded for a 48% response rate (95%CI: 28-69%), including 3/8 with triple negative tumors. Median TTP in MBC is 26+ wk (95%CI: 16-75). 10 pts are ongoing as May 2016. PM01183 pharmacokinetics was unaffected by Xeladon administration.

Conclusions: The combination of PM01183 on D1 with Xel is feasible and has a favorable safety profile. Durable responses occurred in half of MBC pts, confirmatory studies are warranted. Updated data will be presented.

Clinical trial identification: NCT02210364

Legal entity responsible for the study: PharmaMar S.A.

Funding: PharmaMar S.A.

Disclosure: E. Calvo: Consultant or Advisor: Astellas Ph, GlaxoSm, Janssen-Ci, Lilly, Novartis, Pfizer, PharmaMar employee and stock ownership. D. Hyman: Consulting ATARA. E. Calvo: Consulting Astellas Ph, GlaxoSm, Janssen-Ci, Lilly, Novartis, Roche, Sanofi, Symphogen, Taiho. All other authors have declared no conflicts of interest.

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Table: 391P

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<th>Cohort</th>
<th>n = 12</th>
<th>DLT (%)</th>
<th>ORR (%)</th>
<th>DOR months</th>
<th>Tumor Type (%)</th>
<th>CTC-Ali G1-2 (%)</th>
<th>CTC-Ali G3 (%)</th>
<th>Prior Tanes Prior Bev</th>
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<td>A (n = 37/12)</td>
<td>Myelosuppression (%)</td>
<td>40% (14-59)</td>
<td>4.2 (1.2-14.7)</td>
<td>Anemia Fatigue Nausea Vomiting Diarrheas PNI</td>
<td>NSCLC (14); RCC (14); Breast (22); Endometrial (11); EOC (8) (Ovarian (11)); Anemia Fatigue Nausea Vomiting Diarrheas PNI</td>
<td>72 (51-105) 43 (23-135)</td>
<td>28 (21.1-33.3)</td>
<td>28 (21.1-33.3)</td>
</tr>
<tr>
<td>B (n = 12/8)</td>
<td>Myelosuppression (%)</td>
<td>56% (19-61)</td>
<td>6.2 (2-10.8)</td>
<td>Anemia Fatigue Nausea Vomiting Diarrheas PNI</td>
<td>NSCLC (28); RCC (17); Breast (17); Endometrial (11); EOC (8) (Ovarian (11)); Anemia Fatigue Nausea Vomiting Diarrheas PNI</td>
<td>92 (58-142) 33 (17-171)</td>
<td>35 (17-88)</td>
<td>Neutropenia (25)</td>
</tr>
</tbody>
</table>

CL: confidence interval; CTCAE (v4.03), common toxicity criteria adverse reactions (related/unknown); EOC, epithelial ovarian cancer; G, grade; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, overall response rate; PNI, neurotoxicity; FN, febrile neutropenia
Conclusions: MTD for CRLX101 QW monotherapy is 15 mg/m², representing a 100% increase in dose intensity over the QOW MTD. In arm 2, either 12 mg/m² QW or 15 mg/m² for 3 of 4 weeks in combination with bev QOW could be the MTD. No new safety concerns were observed except an increase in cystitis in arm 2 for which urine alkalisation was implemented to mitigate the risk. PKs were observed in 3 pts. This dose-intensive CRLX101 schedule will be tested in future combination studies.

Clinical trial identification: NCT02648711 (NIH)

Legal entity responsible for the study: Cerulean Pharma, Inc.

Funding: Cerulean Pharma Inc.

Disclosure: N. Lakhani: Non-financial support from Cerulean, during the conduct of the study; non-financial support from Cerulean, Merck,Pfizer, Abbvie, ArQule Pharma, Regeneron Pharma,Novartis, BMS, Foundation Medicine, LAM Therapeutics, Prolonai outside the submitted work. All other authors have declared no conflicts of interest.

Table: 395P

**Phase 1 dose-escalation study of the folic acid-tubulysin small-molecule drug conjugate (SMDC) folate-tubulysin EC1456: Study update**

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**Background:** The folate receptor (FR) is highly expressed in certain cancers such as adenocarcinoma and non-small cell lung cancer (NSCLC), but is expressed at low levels in most normal tissues. FR constitutively cycles from the plasma membrane surface to the cytoplasm. In vitro and in vivo studies show the average FR recycling time to be about 18 hours. EC1456 is a potent second generation small molecule drug conjugate (SMDC) of folic acid and the cytotoxic tubulysin B hydrazide (TubBH). EC1456 targets FR-expressing cancers for intracellular delivery of TubBH which inhibits tubulin polymerization in tumors.

**Methods:** The primary objective is to determine the MTD of EC1456 and optimize the dosing schedule. Key inclusion criteria are age ≥ 18 years, ECOG PS 0–1, and adequate end-organ function. Dose escalation follows the 3+3 design. Dose levels are increased with each escalation step. Patient safety is determined using common toxicity criteria. All AEs are recorded daily throughout the entire study period.

**Results:** In an unselected population, 55 patients (pts) are evaluable for cycle 1 toxicity. The median age is 69.5 (range: 39-88); 36 patients are female. Toxicities are primarily hematologic, gastrointestinal, and metabolic changes. Two DLTs have been observed: Gr 3 infusion reaction (4.5% of pts), and Gr 3/4 headache (10.0% of pts). Drug safety is summarized in the table below. Durable stable disease of 12 wks or longer has been observed in 10 pts.

**Table: 395P**

<table>
<thead>
<tr>
<th>AE</th>
<th>BIW (n = 29)</th>
<th>BIW (n = 29)</th>
<th>QW (n = 26)</th>
<th>QW (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>28 (96.6%)</td>
<td>21 (72.4%)</td>
<td>26 (100%)</td>
<td>20 (76.9%)</td>
</tr>
<tr>
<td>SAE</td>
<td>9 (31.0%)</td>
<td>3 (10.3%)</td>
<td>12 (46.2%)</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>Gr 3/4 AE</td>
<td>16 (55.2%)</td>
<td>5 (17.2%)</td>
<td>13 (50.0%)</td>
<td>4 (15.4%)</td>
</tr>
<tr>
<td>Dose Reduction</td>
<td>1 (3.4%)</td>
<td>1 (3.4%)</td>
<td>1 (3.8%)</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>2 (7.7%)</td>
<td>2 (7.7%)</td>
</tr>
</tbody>
</table>

Conclusions: To date, all EC1456 schedules have been well tolerated. Dose escalation is ongoing. Antitumor activity of EC1456 is suggested by durable stable disease. Updated pharmacokinetic, safety, and efficacy analyses will be available for the conference.

Clinical trial identification: NCT01999738

Legal entity responsible for the study: Sponsor is Endocyte, Inc.

Funding: Endocyte, Inc.

Disclosure: A. Armour: Employee of Endocyte, Inc. All other authors have declared no conflicts of interest.
RX-3117, an oral antimitabolite to treat advanced solid tumors (ST): Phase I and ongoing phase 2a results

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Background: RX-3117 is an oral small-molecule antimitabolite, cyclopentenyl pyrimidyl nucleoside, that is activated by uridine cytidine kinase 2. RX-3117 shows efficacy in various xenograft models, including some of genomically resistant pancreatic, bladder and colorectal cancers. Data from a Phase 1/2a clinical study of RX-3117 as a single agent in subjects with advanced ST are described below.

Methods: The Phase 1/2a study (NCT02300067) is designed to evaluate safety, tolerability and pharmacokinetics (PK) following increasing doses and schedules of RX-3117 in eligible subjects (aged ≥ 18 years) with relapsed/refractory ST. Primary objectives include safety and tolerability to determine the MTD and a recommended phase 2 dose and schedule (RP2D). Secondary objectives were PK and antitumor activity. Subjects received oral RX-3117 at 3, 5 or 7 mg per week for 3 weeks with 1 week of rest in each 4 week cycle. Phase 2a is ongoing in patients with metastatic pancreatic or bladder cancer in a 2-stage design, where 10 patients will be treated and if 2 responses are seen, 40 additional patients will be added to the corresponding arm.

Results: As of May 2016, 48 subjects were enrolled (30 Females, 18 males), with 4 subjects enrolled in the Phase 2a portion. Sixteen subjects experienced stable disease for 1 to 10 cycles, with 11 subjects treated from 82 to 276 days. A tumor burden reduction was seen in 3 subjects with pancreatic, breast and mesothelioma cancers. RX-3117 PK was dose proportional and was rapidly absorbed with a median T_{max} of 2 to 3 hours, accumulation was minimal. The most frequent related adverse events were moderate to severe anemia, mild to moderate fatigue and nausea, mild diarrhea, vomiting, and anorexia. Dose limiting toxicity of anemia was observed at 2000 mg administered 3 times per week. The RP2D is 700 mg for 5 consecutive days per week, 3 weeks on, one week off of each 4 week cycle. The most common drug-related adverse events were moderate to severe anemia (23%). All AEs/DLTs were manageable and resolved. Results are presented below.

Conclusions: RX-3117 is safe and well tolerated. Early anti-tumor activity has been observed in pancreas, colorectal and mesothelioma cancers. The 2-stage Phase 2a trial for pancreatic and bladder cancers is ongoing. Final results from the phase 1 and data on the first stage of the Phase 2a will be presented.

Clinical trial identification: NCT02300067

Legal entity responsible for the study: Rexahn Pharmaceuticals, Inc

Funding: Rexahn Pharmaceuticals, Inc

Disclosure: C. Peterson, R. Mazhari, E. Benaim: Employee of Rexahn Pharmaceuticals, Inc All other authors have declared no conflicts of interest.

Phase I study of sorafenib and erubulin in patients with advanced, metastatic or refractory solid tumors

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Background: Combining sorafenib (SOR), an oral multikinase inhibitor approved for hepatocellular carcinoma, renal cell carcinoma, and differentiated thyroid carcinoma, with erubulin mesylate (ERI), a microtubule inhibitor approved for breast cancer (BC), may provide synergistic antitumor activities.

Methods: This phase 1b, open label, dose escalation study evaluated safety, pharmacokinetics (PK), maximum tolerated dose/recommended phase 2 dose (MTD/ RP2D), cardiac safety (QTc/QTcF), and preliminary efficacy of SOR + standard dose ERI (14 mg/kg IV on Days [D] 1 and 8 of each 21 day cycle [C]) in patients (pts) with advanced, metastatic, or refractory tumors. Starting SOR dose was 200 mg BID continuously starting on D1 of C1. SOR + ERI related hematologic and nonhematologic dose limiting toxicities (DLT) were assessed in C2. If tolerable, SOR was escalated in new cohorts to 600 mg daily (200 mg AM/400 mg PM) and 400 mg BID dose proportions. Antitumor activity was assessed by RECIST v1.1. RP2D was confirmed in a MTD expansion cohort (minimum 12 pts).

Results: Of 40 pts treated, 5 received SOR 200 mg BID, 8 received 600 mg/d, and 27 received 400 mg BID (MTD), of whom 14 were in the expansion cohort. Of 12 cancer types reported, 62.5% of pts had BC. No DLT was reported in the 200- and 600-mg cohorts, 1 DLT (Grade 3 increased ALT) was reported in the 400-mg BID dose escalation cohort and 1 DLT (Grade 3 acute coronary syndrome) in the expansion cohort. Most common drug-related ≥ Grade 3 TEAEs were hypophosphatemia (10%) and hypertension (10%) for SOR and neutropenia (25%) for ERI. No significant QTc prolongation was observed; mean QTcF change from baseline was 11.4 ms with ERI alone and 8.25 ms with ERI + SOR. No drug interaction was observed, mean SOR AUC was 60.4 µg*h/L for SOR 400 mg BID + ERI and 56.7 µg*h/L for SOR 400 mg BID alone. Respective mean SOR Cmax were 6.8 and 7.7 µg/L. 9 pts had a partial response (5 confirmed, 3 unconfirmed).

Conclusions: SOR 400 mg BID + standard dose ERI was well tolerated and confirmed RP2D. Toxicities were in line with known SOR and ERI safety profiles. Thus, SOR + ERI would be appropriate to examine in larger studies.

Clinical trial identification: NCT01585870, EudraCT: 2011-005849-12

Legal entity responsible for the study: N/A

Funding: Pharmaceutical Division of Bayer

Phase Ib/II trial of NC-6004 (nanoparticle cisplatin) plus gemcitabine (G) in pts with advanced solid tumors

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Background: NC-6004 is a micromicelle exhibiting sustained release of cisplatin (CDDP) and selective distribution to tumors, resulting in a lower plasma Cmax and higher AUC. Preclinical data exhibited less neuro- and nephrotoxicity with greater anti-tumor activity versus CDDP. A previous trial evaluated NC-6004 and G defining a RP2D of 90 mg/m2. Escalating doses of NC-6004/G were evaluated in this trial using a Bayesian NCRM.

Methods: Pts with refractory solid tumors were enrolled at 4 US sites. NC-6004 at 60 - 180 mg/m2 IV was given over 1 hr on day 1 with G at 1250 mg/m2 IV over 30 mins on day 1 and day 8 every 3 wks. Escalation of NC-6004 began with a single pt run-in, escalating by 15 mg/m2 until a DLT occurred at 180 mg/m2. Cohorts of 4 pts were then enrolled at each dose predicted by the NCRM model with real time updates. The MTD was defined as the dose with the greatest posterior probability of target toxicity < 25%.

Results: Among 22 pts (10 M, 12 F) enrolled, common Grade 3/4 hematologic AEs were leukopenia (67%), thrombocytopenia (55%), neutropenia (55%), lymphopenia (45%) and anemia (23%). All AEs/DLTs were manageable and resolved. Results are presented below (19/22 evaluable for response). Activity was observed in heavily pretreated pts (mean = 2.5 prior lines of therapy). tumor shrinkage in 9/19 (47%), unconfirmed PRs in 3/19 (16%) in H&N and NSCLC pts (1 who failed prior anti-PD1) and SD in 12/19 (63%). The MTD was 135 mg/m2. Of 8 pts treated at the MTD, the average number of cycles received was 7 (2-17) and none experienced neuro-, oto- or nephrotoxicity. 30% of pts received a prior platinum. Of these, SD was observed in 9 (82%).

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Best tumor shrinkage (%)</th>
<th>DLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>-16.7</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>135</td>
<td>0</td>
<td>-45.3</td>
</tr>
<tr>
<td>150</td>
<td>32.6</td>
<td>-15.2</td>
</tr>
<tr>
<td>180</td>
<td>26</td>
<td>-60.4</td>
</tr>
<tr>
<td>210</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>-3.3</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>320</td>
<td>-22</td>
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</tr>
<tr>
<td>350</td>
<td>-19.4</td>
<td></td>
</tr>
<tr>
<td>400</td>
<td>-49.1</td>
<td></td>
</tr>
</tbody>
</table>

|                |                        |      |
|                | Thrombocytopenia       |      |
|                | Thrombocytopenia       |      |

Table: 398P

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Conclusions: The nanoparticle formulation allowed greater CDDP equivalent doses. No clinically significant neuro-, oto- or nephrotoxicity was observed. The NCRM design allowed exploration of the pharmacologic zone of interest and projected a higher MTD versus a 3 + 3. This data demonstrates promising activity and tolerability of NC-6004/G in heavily pretreated pts.

Clinical trial identification: NCT0173913 (NIH register)

Legal entity responsible for the study: The Netherlands Cancer Institute

Funding: The Netherlands Cancer Institute

Disclosure: B. Nijm: Is holder of a patent of oral formulations of taxanes and shareholder of Modra Pharmaceuticals, a company developing oral taxane formulations. All other authors have declared no conflicts of interest.

Correlations for tested doses and toxicities between first-in-human trials and registration trials of FDA-approved monoclonal antibodies (mAb) over a decade: due to mAb limited toxicity, the recommended phase II dose (RP2D) was only tentatively defined in first-in-human trials (FIHT), and the FIHT RP2D and the maximum administered doses (MAD) were infrequently used in subsequent trials. In contrast, for cancer drugs in general, FIHT results are predictive of safety in registration trials (RT) and of approved drug dose (Jardim et al, Clin Cancer Res 2014).

Methods: In order to determine the correlations of mAb FIHT results with safety in RT and final approved dose, we identified mAb approved as single agents by FDA on March 1, 2016. For each molecule, we performed a MEDLINE search to identify FIHT and RT, and then we examined the doses tested and the toxicities observed in RT with regard to the corresponding FIHT results.

Results: We retrieved 28 mAbs with a FIHT, and 60 RT. The mAb indication was cancer in 11 cases (solid tumors in 8, hematological cancers in 3), immune system diseases in 13 cases and other diseases in 4 cases. In FIHT, the RP2D was determined in 5 cancer trials (v.s 2 in the other trials). For mAb with the same dose calculation in FIHT and RT, the RP2D was tested in cancer RT in only 5 cases, and the MAD in 2 cases (vs 1 and 2 cases respectively in the other trials). The median ratio between cancer RT dose and the corresponding MAD was 0.5 (n = 9; range: 0.2 to 2.3), versus 0.67 in the other trials (n = 13; range: 0.1 to 1.2). Seven out of 11 doses tested in cancer RT were of less than 75% of the MAD, with 4 RT doses of less than 50% of the MAD. Grade 3/4 toxicities were infrequent. No statistically significant concordance for grade 3/4 toxicities between RT and FIHT was observed.

Conclusions: These data show a major discrepancy between RP2D and MAD of mAb FIHT when compared with doses tested in RT, and toxicities detected in mAb FIHT do not correlate with RT toxicities. As FIHT data inform only partially choices of RT doses, rational strategies for mAb dose selection in the clinical setting remain an unmet need.

Legal entity responsible for the study: ICM Montpellier

Funding: ICM Montpellier

Disclosure: C. Gongora: Research funding from Novartis, Astellas and Janssen travel funding from Lilly. L. Li: Activity as consultant or advisor board member: Roche, GlaxoSmithKline, Pfizer, Boehringer Ingelheim, Celgene, Takeda Pharmaceutical, Taiiana Pharma, Synthion, AstraZeneca, Genomic Health, Merck Sharp & Dohme, Synaffix. D. Tosi: Research funding from Novartis, Astellas and Janssen travel funding from Bayer, Janssen, Astellas, Sanofi. All other authors have declared no conflicts of interest.

The use of next generation sequencing (NGS) to guide patient selection for phase 1 clinical trials

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Background: Therapeutically targeting actionable mutations in cancer may increase response rates in Phase I clinical trials. We undertook a pilot study to assess the feasibility and therapeutic benefit of incorporating NGS screening into the patient pathway for phase 1 cancer trials.

Methods: NGS tumour profiling was performed using a 22 gene amplicon-based panel (Life Technologies Colon & Lung V2) on 117 consecutive patients (pts) referred over a 13 month period for Phase I trials. BRCA1/2 analysis was performed in pts with epithelial ovarian cancer.

Results: 117 pts (67% female) with a median age of 59 (range 22-78) years were included. Common tumour types were ovarian (n = 20), colorectal (n = 16), breast (n = 13), endometrial (n = 12) and lung (n = 8) cancer. NGS was successfully performed in 108 (92%) pts with a median time to results of 12 days (range 6-39), 82% of pts (89/108) had a detected variant in ≥ 1 gene with an average of 3 variants (range 0-26) in 2 genes (0-10) per case. Common mutations included TP53 (69%), KRAS (14%), PIK3CA (11%) and SMAD4 (9%); BCCAI/2 mutations were present in 11 (55%) ovarian cancer pts. Overall, 49 (45%) pts had ≥ 1 actionable mutation. Detected variants were reviewed in a local genomics review board to assess actionability prior to considering therapy: 53 pts were commenced on a Phase I trial; 18 (34%) were genotype directed. Median duration on trial was 73 days for pts on genotype (7-260) days or non-genotype (20-382) directed trials with 50% and 24% of allocated patients continuing on study respectively. Of pts evaluable for response (n = 47), partial response (PR), stable disease (SD) and progressive disease (PD) were observed in 50%, 29% and 21% of pts on genotype directed trials and 20%, 37% and 43% of pts on non-genotype directed respectively. Excluding pts on BCCAI/2 directed trials, PR, SD and PD were observed in 33%, 33% and 33% of pts respectively in genotype-directed studies.

Conclusions: NGS is feasible in real time and may affect clinical outcome in the phase 1 setting. Almost half of pts had a potentially actionable mutation. Initial response rates for pts treated on genotype-driven trials are encouraging. Benefit is likely to be augmented using a broader NGS panel which is planned for future assessment.
Genomics Program enrolment. was low. Prior molecular profiling was not an independent predictor of clinical trial had prior molecular profiling, the proportion subsequently enrolled into clinical trials with higher likelihood of trial enrolment (all p < 0.05).

Background: Phase I trials increasingly use molecular enrichment for patient selection. In 2012, we initiated a molecular screening program at Princess Margaret (PM) Cancer Centre using either a customized multi-gene hotspot panel or targeted next-generation sequencing to match patients with actionable mutations to clinical trials. Our aim was to evaluate the outcome of new patient referrals seen in the PM phase I clinic and factors associated with subsequent clinical trial enrolment.

Methods: A retrospective chart analysis for consecutive PM phase I clinic new referrals from May 2012 and December 2014. Data on their demographics, prior molecular profiling results, medical history, and details of clinical trial participation or non-entry were recorded.

Results: Of 941 new patient referrals 560 (58%) patients were offered ≥1 clinical trials and 265 (28%) were subsequently enrolled. The most common reasons that patients were not trial candidates included poor performance status (37%), medical comorbidities (17%), other treatment preferred (16%) and ongoing systemic treatment (8%). There were 396 (42%) new referrals that had prior molecular profiling with no increase in the proportion of referrals with prior molecular profiling over time (p = 0.42). Patients with prior molecular profiling were younger, more heavily pre-treated with systemic therapies, with better Princess Margaret Prognostic Index (albumin <35g/L, >2 metastatic sites, and ECOG performance status (PS) >0) scores, and lived closer to PM than patients who did not undergo prior molecular profiling (all p < 0.01). Patients with molecular profiling were more likely to be offered clinical trials (68% vs 51%, p < 0.001) and subsequently enrolled (33% vs 23%, p < 0.001). In multi-variable analysis, only PS (0/1 vs 2/3), disease site (non-GI vs GI), distance to PM (<50km vs ≥50km), and referring physician (internal vs external) were associated with higher likelihood of trial enrolment (all p < 0.05).

Conclusions: Although close to one-half of new patients referred to a phase I clinic had prior molecular profiling, the proportion subsequently enrolled into clinical trials was low. Prior molecular profiling was not an independent predictor of clinical trial enrolment.

Clinical trial identification: 15-K073-3E

Legal entity responsible for the study: Princess Margaret Cancer Centre - Cancer Genomics Program

Funding: Princess Margaret Cancer Genomics Program

Disclosure: All authors have declared no conflicts of interest.

Clinical outcomes and predicting early death in early phase trials: The NIHR UCLH clinical research facility (CRF) experience

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Background: Early phase trials provide dose finding, toxicity, pharmacokinetic, pharmacodynamic, and preliminary efficacy data for novel drugs, as well as treatment options for advanced cancer patients when standard therapies are exhausted. Patients must be carefully selected to ensure robust data.

Methods: We retrospectively identified patients with advanced cancer treated in early phase trials at the NIHR UCLH CRF from April 2010 to April 2015. Demographic, clinical and survival data were collected. Multivariate analysis (MVA) examined the relationship between baseline variables and survival, and compared these with known prognostic scores (CHAD, Hammersmith (HS), Royal Marsden (RMH) for Phase (PH) I trials).

Results: 296 patients (PH 1: 216; PH 2: 80) were included. Median age 61 (range 21-83), 57% male. Baseline PS: 0 27%, 1 60%, tumour type: Breast/gynae 32%, hepatobiliary 29%. Median lines of prior systemic therapy: 2 (0-9). Overall response rate 13.5% (PH 1: 12.1%; PH 2: 17%). Survival: CR (PS 1) 12.0% (CR 1: 12.0%; 12.0% PH 2). Median overall survival was 10.3 months (mo) (0.5-76.4). PH 1 8.6 mo (0.5-53.5) and PH 2 16.8 mo (0.7-76.4). The 90 day mortality (90DM) was 10.8% (12.5% PH 1; 6.3% PH 2). Predictors of 90DM were explored for the PH 1 group. CHAD, HS, and RMH scores had limited discriminative ability for predicting 90DM (area under the ROC curve (AUROC): CHAD 59.4% (95%CI 50.6-68.6), 63.6% (53.2-74), 60.7% (50.2-71.1) respectively). MVA of our data identified low albumin (OR 4.7%, p = 0.004) and raised LDH (OR 4.37, p = 0.016) as significantly associated with early death. When combined to form a score, the AUROC was 70.9% (61.8-80.3) but as with the other scores was neither sensitive nor specific for clinical decision making.

Conclusions: A modest number of patients in early-phase trials have significant tumour response. Prognostic scores to identify patients at risk of 90DM in early phase trials appear ineffective within the heterogeneous early phase trial population. Trial inclusion criteria should be tailored to the drug and tumour-type under investigation to filter unsuitable patients.

Legal entity responsible for the study: NIHR UCLH Clinical Research Facility

Funding: NIHR UCLH Clinical Research Facility

Disclosure: All authors have declared no conflicts of interest.

Clinical outcome of patients with advanced biliary tract cancer in a dedicated phase 1 unit


Drug Development Unit, Institute of Cancer Research ICR, London, UK

Background: Advanced biliary tract carcinomas (ABC) are fatal malignancies with limited effective therapeutic alternatives for advanced disease. Following first line treatment, clinical trials using experimental novel therapeutic agents may be considered for selected patients. This study describes the experience of ABC patients treated in a specialized phase 1 unit.

Methods: Patient characteristics, tumour features, treatment details and clinical outcomes of ABC patients treated at the Drug Development Unit, Royal Marsden Hospital, between 2002 and 2016, were captured and analysed from case and trial records.

Results: 123 ABC patients were included in the study, of which 48 patients participated in 41 different phase 1 trials. Patients had a median of 2 previous lines of systemic chemotherapy (range 1-6). 4% (17) entered a second phase 1 study upon progression on the first study. 15% (31%) had molecular characterization of tumours using a targeted panel, yielding 7 potentially actionable mutations including BRCA (2), PIK3CA (2), FGFR, AKT and PTEN loss. However, due to logistical reasons, none of them received treatment on a trial matched to these mutations. Of the 39 evaluable patients, there was one exceptional responder who had a partial response (PR) that continues to be maintained at 1.5 years on a PARP inhibitor study. 18 patients (46%) achieved stable disease (SD) as their best response, and this was sustained for more than 6 cycles (18 weeks) in 4 patients (8%). Median progression free survival was 6.1 weeks (95% CI 3.3 – 9.3) and median overall survival was 22.0 weeks (95% CI 18.8 – 25.2). Treatment was generally well tolerated with grade 4 or 5 adverse events only observed in 8 patients (17%) of which 6 were drug related and led to trial discontinuation in 1 (3%), with no toxicity related deaths.

Conclusions: Experimental phase 1 clinical trials are a reasonable and safe alternative for selected patients with ABC. Several actionable mutations were identified by our targeted panel, however due to logistical reasons none were enrolled onto matched trials. Future work requires more comprehensive molecular profiling to understand the biology underlying the exceptional response, to identify new treatment options, and to match patients in real-time to targeted therapies.

Legal entity responsible for the study: Institute of Cancer Research

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Patients with metastatic prostate cancer enrolled in phase 1 trials: Outcomes and molecular alterations

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Background: The purpose was to describe characteristics of patients (pts) with castration-resistant prostate cancer (CRPC) referred to phase I unit for phase 1 trials or molecular screening programs.

Methods: All patients enrolled in clinical trials in the Gustave Roussy phase 1 unit (DITEP) from 2006 until April 2016 were reviewed. Baseline characteristics, PSA response, progression-free survival (PFS) and overall survival (OS) were investigated. Molecular alterations (MA) were collected from MOSCATO trial database comprising 1168 patients screened for genomic characteristics.

Results: Ninety-three pts had CRPC, enrolled in 30 different trials. At baseline, median age was 68.5y (63.5 – 73.0), 62 pts (66.7%) had an OMS PS 1, median PSA was 96 (32.9
Dose affect tumour response in Phase I oncology trials of non-cytotoxic agents? J. Ghosh1, G. Lazaridou1, Z. Viney1, H. Verma1, I. Sheff2, Y. Wang1, H. Moller1, J. F. Spicer3, D. Sarker1

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Background: Although phase I oncology trials have conventionally used the maximum tolerated dose (MTD) as the recommended dose for phase II studies (RP2D), there is conflicting data on how dose relates to response for non-cytotoxic agents. Also, patients achieving disease stabilisation have differing tumour growth rates (TGR). We retrospectively evaluated tumour response and kinetics at different dose levels in phase I trials.

Methods: All patients enrolled in phase I trials of non-cytotoxic in a single UK centre between 2007-2015 were evaluated. Patients were divided into four dose levels (<40%, 40-60%, 60-80%, >80%) based on the percentage of the dose allocated to the maximum administered dose (MAD) on the trial. TGR was measured as the percentage change in tumour volume per unit time.

Results: A total of 151 patients were enrolled in 12 phase I trials (8 molecularly targeted agents, 3 immunotherapy and 1 steroid synthesis inhibitor). Median age was 59 years and 73% had low risk RHM score. There was no statistically significant difference in best response on treatment, progression free survival (PFS) or overall survival (OS) at different dose levels. Increased toxicity resulting in dose reduction or treatment discontinuation was seen at higher doses. However, when responders (complete or partial response, or stable disease) were analysed separately, higher doses were associated with of decreasing TGR, longer median PFS and OS (Table).

Conclusions: Overall for non-cytotoxic agents there was no significant dose-response relationship but the subgroup of responding patients had longer survival at higher doses. Thus MTD should continue to be the RP2D though there is need for aptor identifying potential responders.

Table: 406P - Response, toxicity, progression free and overall survival at different dose levels

<table>
<thead>
<tr>
<th>%MAD</th>
<th>&lt;40 n = 22</th>
<th>40-60 n = 65</th>
<th>&gt;60-80 n = 33</th>
<th>&gt;80 n = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Response Complete/Partial Response Stable Disease</td>
<td>14% 27%</td>
<td>12% 48%</td>
<td>24% 30%</td>
<td>23% 16% p = 0.17</td>
</tr>
<tr>
<td>TGR at Best Response (Responders)</td>
<td>0%</td>
<td>-14%</td>
<td>-8%</td>
<td>-30% p trend = 0.017</td>
</tr>
<tr>
<td>Toxicity Dose Reduction Drug Discontinuation</td>
<td>0 0</td>
<td>5% 15%</td>
<td>21% 9%</td>
<td>16% 13% p = 0.017</td>
</tr>
<tr>
<td>Median PFS (weeks) All Patients Responders</td>
<td>16 20</td>
<td>16 20</td>
<td>13 29</td>
<td>9 (p = 0.16) 36 (p = 0.002)</td>
</tr>
<tr>
<td>Median OS (weeks) All Patients Responders</td>
<td>27 44</td>
<td>47 54</td>
<td>43 73</td>
<td>32 (p = 0.137) 108 (p = 0.24)</td>
</tr>
</tbody>
</table>

Legal entity responsible for the study: N/A

Funding: No funding was required as this was a retrospective study

Disclosure: All authors have declared no conflicts of interest.
The TRK family of neurotrophin receptors (TRKA, TRKB, and TRKC) encoded by NTRK1, NTRK2, and NTRK3 genes, respectively) and their ligands involve the kinase domain are oncogenic and have been identified across common primaries for whom neurosurgical resection would be standard of care. After a phase 1b safety run-in, the phase 2 part of the trial randomises patients (n = 60) into 3 arms: afatinib alone for 11 days, then neurosurgery on day 12; afatinib alone for 11 days plus a single 4 Gy fraction on day 10, then neurosurgery on day 12; afatinib for 11 days plus a single 4 Gy fraction on day 10, then neurosurgery on day 12

Table: 408TIP

<table>
<thead>
<tr>
<th>Armp</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: afatinib alone for 11 days, then neurosurgery on day 12</td>
<td></td>
</tr>
<tr>
<td>Arm 2: afatinib for 11 days plus a single 4 Gy fraction on day 10, then neurosurgery on day 12</td>
<td></td>
</tr>
<tr>
<td>Arm 3: afatinib for 11 days plus a single 4 Gy fraction on day 10, then neurosurgery on day 12</td>
<td></td>
</tr>
</tbody>
</table>

The primary endpoint is to compare steady-state afatinib concentration in recesed brain mets, following afatinib administered alone, or in combination with radiotherapy (2 Gy or 4 Gy). Afatinib concentrations are measured in the resected brain mets and in plasma. Secondary endpoints: safety of afatinib administration in combination with radiotherapy; and multi-sequence MRI (optional) to detect changes in perfusion, vascular density, blood-betain and interstitial pressure. Exploratory endpoints: molecular profiling of resected brain mets, for comparison with paired primary lung and breast cancers; the study of patient-derived xenografts. CamBMT1 is a multi-centre trial now opening at additional Experimental Cancer Medicine Centres, and is funded by Cancer Research UK, the Brain Tumour Charity and Boehringer-Ingelheim.

Clinical trial identification: EudraCT Number: 2013-002397-23

Legal entity responsible for the study: Cancer Research UK Foundation Trust and the University of Cambridge

Funding: Cancer Research UK The Brain Tumour Charity Boehringer-Ingelheim

Disclosure: All authors have declared no conflicts of interest.

A phase II basket study of the oral TRK inhibitor LOXO–101 in adult subjects with NTRK fusion-positive tumors

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Background: The TRK family of neurotrophin receptors (TRKA, TRKB, and TRKC encoded by NTRK1, NTRK2, and NTRK3 genes, respectively) and their ligands involve the kinase domain are oncogenic and have been identified across common tumor types. Fusions of NTRK genes which involve the kinase domain are oncogenic and have been identified across common tumor types. Fusions occur at a frequency of <5% in common malignancies (breast, lung, colon) but have been identified in 75% of cases of rare tumor types such as mammary analogue secretory carcinoma (MACS) of the salivary gland and secretory breast carcinoma. LOXO-101 is the only selective pan-TRK inhibitor in development, with IC50 values in the low nanomolar range for inhibition of TRK family members in binding and cellular assays and with 1000x selectivity over other kinases. Anti-tumor activity and symptomatic improvement within 8 weeks of drug initiation have been seen in 6 evaluable NTRK fusion-positive patients with varying histologies enrolled to an ongoing adult phase 1 trial; confirmed RECIST responses have been seen in 5 of those 6 patients. No responding patients had progressed as of data cutoff and the longest response duration has been in excess of 14 months. Anti-tumor activity has been seen at and below the RP2D of 100mg BID.

Trial design: The phase II global study of LOXO–101 (NCT02576431) is an open-label, multi-center trial for patients with any type of advanced solid tumor or primary CNS malignancy harboring an NTRK fusion. Patients age 12 and older with NTRK1, 2, or 3 fusion-positive solid tumors who have progressed following standard therapy are eligible. Prior progression with an investigational or approved agent targeting TRK is an exclusion, intolerance to a prior inhibitor is allowed. The primary endpoint of the study is overall response rate by RECIST 1.1 or RANO. Key secondary endpoints include duration of response, percent tumor regression as best response, PFS and duration of OS. Patients undergo radiographic evaluation for their disease at regular intervals. LOXO-101 is administered orally BID in capsule form starting at 100mg for continuous 28-day cycles. Archival tissue and/ or fresh tissue are required for future molecular assessment.

Clinical trial identification: NCT 02576431 release date: 12 October 2015 EudraCT 2015-003582-28 release date: 14 April 2016

Legal entity responsible for the study: Loxo Oncology, Inc.

Funding: Loxo Oncology, Inc

Disclosure: D. Hong: Travel support from Loxo Oncology, Inc. S. Smith, M. Reynolds, S. Cruickshank: Paid consultant for Loxo Oncology, Inc. M. Deegan, N. Ku: Employee and stockholder of Loxo Oncology, Inc. All other authors have declared no conflicts of interest.

Phase 2, open-label study of ceritinib in patients (pts) with advanced non-lung solid tumors and hematological malignancies characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK) using a flexible adaptive design: ASCEND-10

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Background: Genetic alterations in ALK are found in subsets of several cancers. In vitro and in vivo experiments have shown that neuroblastoma, anaplastic large cell lymphoma (ALCL) and non-small cell lung cancer (NSCLC) models carrying ALK alterations are sensitive to ALK inhibitors. In the ASCEND-1 study, pts with ALK+ ALCL (n = 57) showed a dramatic response to ceritinib (Ridley H et al. Blood 2015). Ceritinib also demonstrated antitumor activity in pediatric pts with ALK+ inflammatory myofibroblastic tumor (IMT) and ALCL (NCT01742286). These data provide a rationale to assess ceritinib in diverse ALK+ tumors other than NSCLC.

Trial design: ASCEND-10 is a prospective, open-label, multicenter, multi-arm study (NCT02465528) designed primarily to evaluate activity based on disease control rate (DCR) at 16 weeks by investigator in pts with advanced ALK+ non-lung solid tumors and ALK+ hematologic malignancies. Key secondary objectives: investigator-assessed ORR, DOR, time to response and overall safety. This trial will enroll adult pts with locally tested ALK gene aberrations. Eligible pts must have received ≥2 line of prior systemic treatment, provide an archival or fresh tissue prior to first dose. Other exclusion criteria: pre-existing cardiac disease, history of interstitial lung disease, and/or other significant cardiac, pulmonary, renal, hepatic, or neurologic disease. The primary endpoint of the study is overall response rate by RECIST 1.1 or WHO Pts ≥ 2. There will be ≥4 different tumor types (TT) in parallel arms: ALCL, IMT, glioblastoma, inflammatory breast cancer and any other non-ALK+ tumor. An adaptive design using a Bayesian Hierarchical model (BHM) will be used for the analysis of DCR. Proposed design is adaptive in the sense that it allows borrowing information from other TT if efficacy is similar and provide more precise estimate of DCR. Early termination of a specific TT due to lack of efficacy is permitted. This flexible design also allows separate interim and final analysis for each TT once accrual and follow-up are complete for a given TT. Due to adaptive nature of the design the final sample size is not fixed. Approximately 106 pts are planned to be enrolled in this study.

Clinical trial identification: NCT01742286

Legal entity responsible for the study: Novartis Pharmaceutical Corporation

Funding: Novartis Pharmaceutical Corporation
First-in-human trial of 4'-thio-2'-deoxycytidine (TdCyd) in patients with advanced solid tumors

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Background: Methylation-mediated silencing of genes is an epigenetic mechanism implicated in tumourigenesis. Hypermethylating agents such as 5-aza-deoxycytidine (5-aza-Cyd) act following internalisation of EDVs. EDVs are also taken up by immune system cells and stimulate the adaptive immune response resulting in a two-pronged anti-tumor approach. EGFR-targeted EDVs carrying mir15/16 mimics are currently being tested following internalisation of EDVs. EDVs are also taken up by immune system cells and stimulate the adaptive immune response resulting in a two-pronged anti-tumor approach. EGFR-targeted EDVs carrying mir15/16 mimics are currently being tested in several tumour xenografts. Depletion of DNTM1 was observed also in certain xenograft models.

Trial design: We are conducting an open label phase 1 first-in-human trial of TdCyd, following an accelerated titration design. TdCyd is administered PO qd x 5 days of each week for up to 21 days. The primary objective of the study is to establish its safety, tolerability, maximum tolerated dose, and recommended phase 2 dose. The secondary objectives of the study are to evaluate the CD3 + T cell expansion, measured by flow cytometry, and changes in EGFR expression.

Eligibility criteria: solid tumor patients whose disease has progressed on standard therapy, ECOG ≤ 2, and normal organ function. Blood samples for PK/PD analyses and expression of CTCS in CTCS are being evaluated. Currently, we are enrolling at DLS in the escalation portion of the trial.

Clinical trial identification: NCT02428057

Legal entity responsible for the study: Division of Cancer Treatment and Diagnosis, National Cancer Institute

Funding: National Cancer Institute

Disclosure: All authors have declared no conflicts of interest.

The Tailored EDVTM trial: A phase I feasibility study evaluating EGFR-targeted EDVTM nanocells as a therapy platform in patients with refractory advanced solid tumours

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Background: EnGeneIC has developed the EDVTM – Nanocell Platform Technology (Ezrik Vector), which is a First-in-Class CytoImmuno-Therapy for the treatment of solid cancers. Cytotoxic drug, siRNA or miRNA are packaged into EDV nanoparticles targeted to cancer cells via antibodies and payload is delivered intracellularly following internalisation of EDVs. EDVs are also taken up by immune system cells and stimulate the adaptive immune response resulting in a two-pronged anti-tumor approach. EGFR-targeted EDVs carrying mti15/16 mimics are currently being tested in a Phase 1 trial, with objective responses and prolonged disease control seen in refractory mesothelioma patients. The hypothesis for this Tailored EDV trial is that dosing patients with EGFR targeted-EDVs (EGFEDVs) with a payload tailored to an individual patient’s tumor will result in enhanced anti-tumor effects, overcoming established drug resistance.

Trial design: An open-label Phase I feasibility study of a single delivery agent EDVs containing clinic choice therapeutic payload(s) (cytotoxic drug, siRNA or miRNA) in subjects with advanced solid tumours who have failed standard treatments. The trial opened at the Northern Cancer Institute, Sydney, in August 2015 with 5 patients being recruited to date out of a possible 25 (ANZ CTR number: ACTRN12613001249741). Eligibility criteria include EGFR expression in tumour tissue using immunohistochemistry, measurable disease by standard radiological assessment according to RECIST, ECOG 0-1, and adequate organ function. The study design allows for one dose per week via a 20 minute infusion for 8 weeks. The first dose uses 2x107 nanocells and subsequent doses utilize 5x107 nanocells. Premedication comprises dexamethasone, promethazine and paracetamol and patients are monitored for a minimum period of 3 hours. Response assessments are undertaken at 8 weeks using standard imaging and relevant tumour markers. Exploratory cytokine analysis and analysis of immune cells is included.

Clinical trial identification: ANZ CTR number: ACTRN12613001249741

Legal entity responsible for the study: EnGeneIC Pty Ltd

Funding: EnGeneIC Pty Ltd

Disclosure: S. Sidhu: I am a shareholder of EnGeneC Pty Ltd. H. Brahmbhatt: I am a Director of EnGeneC P/L and hold shares in that entity. J. Macdiarmid: I am a Director of EnGeneC P/L and hold shares in it. All other authors have declared no conflicts of interest.

A dose-escalation study of weekly intravenous CRLX301 in patients with advanced solid tumor malignancies

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Background: Cerulean’s nanoparticle-drug conjugates (NDCs) are designed to enhance delivery of drugs to tumors while sparing healthy tissues and to gradually release drug payloads once inside tumors with the goal of improving antitumor activity and reducing systemic toxicity. CRLX301 is a novel investigational NDC containing the payload docetaxel covalently conjugated to a cycloextrin-polyethylene glycol copolymer currently being investigated in a phase 1/2a study of patients with advanced solid tumors. The first portion of the study determined the maximum tolerated dose (MTD) for intravenous (IV) CRLX301 every 3 weeks (Q3W) to be 75 mg/m2 and showed that CRLX301 was generally well tolerated with hints of antitumor activity and a differentiated pharmacokinetic (PK) compared to docetaxel (Wang H, ASCO 2016. Abs. 2526). This portion aims to determine the MTD for weekly administration (QW) of CRLX301.

Trial design: We will enroll adults with advanced solid tumors, adequate organ function and ECOG Performance Status 0-1. Simulation modeling with the QW PK data suggest that total and released docetaxel will not accumulate in plasma after 9 weeks of QW CRLX301 at 20, 25, 30 or 40 mg/m2. Also, at these doses the estimated total and released docetaxel area under the plasma drug concentration-time curves (AUCs) after the 1st, 4th and 7th doses would not exceed those observed with CRLX301 at 75 mg/m2 Q3W. These results support a weekly starting dose between 20 and 25 mg/m2. Weekly doses will be tested in a 3 + 3 design. The primary objective is to determine the CRLX301 QW MTD. Secondary objectives include assessments of safety, PK and antitumor activity. Serial plasma samples for PK evaluation will be collected during weeks 1, 4, and 7. Tumors will be evaluated every 8 to 9 weeks per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. A recommended phase 2 dose will be determined for use in the phase 2a expansion in patients with specific tumor types, including taxane-naive bladder cancer. Data from QW and Q3W studies will be evaluated to select the optimal dosing schedule for future clinical trials of CRLX301.

Clinical trial identification: NCT02836077 (NIBI)

Legal entity responsible for the study: Cerulean Pharma, Inc.

Funding: Cerulean Pharma, Inc.

Disclosure: H. Wang, C. Murphy, A. Sandlerowski. Employee of Cerulean Pharma Inc. B. Markman, P. de Souza: Grants from Cerulean Pharma Inc. E.C. Dees: Non-financial support and other from Cerulean, during the conduct of the study; other from Pfizer, personal fees and other from Novartis; other from Bayer, Merck, Lilly, Roche, outside the submitted work. T.C. Ganghadar: Grants from Merck, outside the submitted work W.C. Zamboni: Personal fees from Cerulean Pharma, outside the conducted study; personal fees from Cerulean Pharma, outside the submitted work. All other authors have declared no conflicts of interest.

Annals of Oncology

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Background: CUP identifies a heterogeneous clinical and pathological syndrome characterized by absence of an identifiable site-specific tumor of origin, early metastatic dissemination and undifferentiated phenotype. Representing 3-5% of all cancers, CUPs are still an unsolved clinical problem, with elusive biology and paucity of effective therapies. No validated actionable targets and no preferred regimen have emerged so far. With 25-30% response rate (RR) and overall survival (OS) from 6 to 16 months, the current approach is largely suboptimal. The AGNOSTOS project represents a unique clinical and translational initiative aiming to improve the outlook of CUP pts through evaluation of novel chemotherapeutic regimens (AGNOSTOS TRIAL_1) and a better understanding of the complex CUP biology (AGNOSTOS TRASLATIONAL COMPANION STUDY).

Trial design: AGNOSTOS_1 is a randomized phase II trial with a ‘pick the Winner’ design that will assess efficacy of NabPaclitaxel (NabPa) in combination with either Carboplatin (C) or Gemcitabine (G) in treatment-naive CUP pts (EudraCT 2016-005018-47). We plan to enroll 112 pts based on a Simon’s two-stage design. Inclusion criteria include measurable disease and adequate archived biopsy tissue for immunohistochemical and molecular profiles. Patients will receive NabPa 125 mg/m² plus G 1000 mg/m² or C AUC 2 on day 1 and 8 by every 21 days. Tumor response will be assessed every 9 weeks. Primary endpoint is RR while secondary endpoints are time to progression and OS. Furthermore, AGNOSTOS_2 will perform an in-depth characterization of the enrolled CUPs. Vital tissues and liquid biopsies will be collected to derive patient-derived xenografts (PDX) and circulating cancer stem cells, respectively. The comprehensive genetic analysis (by next generation sequencing) aims to pinpoint common denominators of the hypermetastatic phenotype and its molecular link with cancer stemness. Currently we have enrolled 6 pts in AGNOSTOS_1 and 31 in AGNOSTOS_2 (with 8 PDX attempted).

Clinical trial identification: Clinical trial information: NCT02607202

Legal entity responsible for the study: IRCCS Candiolo (ITALY)

Funding: AIBC 5 x 1000, Celgene

Disclosure: S. Siena: Advisory role for Amgen, Roche, Bayer, Ely Lilly, Sanofi, Merck. S. Marsoni: Research funding: Celgene. F. Montemurro: Speaker’s bureau member Astra Zeneca, Roche and Novartis. All other authors have declared no conflicts of interest.
Efficacy and safety of pasireotide LAR or everolimus alone, or in combination in patients with advanced carcinoid (NET) of the lung/thymus: Results from the randomized, phase 2 study

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Background: Advanced lung/thymus carcinoid is an area of high unmet medical need. In recent phase 3 RADIANT-4 study, everolimus (E) showed progression-free survival (PFS) benefit in patients (pts) with GI/lung NET. Pasireotide LAR (P, somatostatin analog (SSA)), has also shown potential antitumor activity in previous studies in NET. This phase 2 study evaluated efficacy and safety of P, E, and P + E in pts with inoperable carcinoid of lung/thymus.

Methods: Adult pts with metastatic RECIST progressive carcinoids of lung/thymus were randomized (1:1:1) to P (60 mg/month [mo] i.m.), E (10 mg/day orally) and P + E. Primary endpoint was progression free rate at mo 9 (PFR-9): proportion of pts at mo 9 with complete (CR), partial (PR) response or stable disease (SD) according to RECIST v1.1. Key secondary endpoints were PFS, disease control rate and safety.

Results: 124 pts were randomized to P (41), E (42), P + E (41). Median age = 64 yrs; atypical/typical carcinoid = 68.5%/31.5%; WHO performance status: 0/1/2 = 64%/34%/0; anti-proliferative activity due to its ability to decrease insulin and IGF1 levels; in association metformin (MET) treatment with a decrease of cancer risk. MET may have anti-proliferative activity due to its ability to decrease insulin and IGF1 levels; in addition, it promotes AMPK activation and TSC1-2/mTOR inhibition. This multicentric, retrospective study evaluates the impact of glycemic status (hyper vs normoglycemia) on progression-free survival (PFS); the impact of concomitant MET administered during EVE and/or SA therapy in diabetic pNETs is also assessed.

Methods: To obtain a 90% statistical power, with a error 0.05, and to detect an HR of 0.67 for hyperglycemic vs normoglycemic pts, 267 events (PD or SA) were planned. With these numbers, the power was anticipated to detect HR 0.67 in each subgroup analysis (hyperglycemic pts on MET vs normoglycemic and on MET vs normoglycemic pts). The phase III trials, both everolimus (EVE), and somatostatin analogues (SSA) have shown antitumor activity in pNETs. Some studies have identified diabetic patients (pts) as having increased risk for the development of cancer and have associated metformin (MET) treatment with a decrease of cancer risk. MET may have anti-proliferative activity due to its ability to decrease insulin and IGF1 levels; in addition, it promotes AMPK activation and TSC1-2/mTOR inhibition. This multicentric, retrospective study evaluates the impact of glycemic status (hyper vs normoglycemia) on progression-free survival (PFS); the impact of concomitant MET administered during EVE and/or SA therapy in diabetic pNETs is also assessed.

Results: Between 1999 and 2016, 445 pts (median age 59, range 49-69; 53.5% males), were treated with EVE and/or SA in 24 Italian Centers. In total, 112 (25.2%) diabetic pts received MET, 91 (20.4%) received INS and 33 (7.7%) received dietetic counseling; 209 (46.7%) pts were normoglycemic. In the overall population, median FBS was 23.4 months (mo) (95% CI 19.1-27.9); mPFS was 32.0 mo in diabetic pts and 15.1 mo in normoglycemic pts (HR 0.63, 95% CI 0.50-0.80; p = 0.0002). Median FBS was 20.8 mo (95% CI 15.6-63.8) in pts receiving INS (HR vs normoglycemic pts 0.81, 95% CI 0.60-1.1, p = 0.18) and 44.2 mo (95% CI 36.4-61.9) in pts on MET (HR vs normoglycemic pts 0.43, 95% CI 0.32-0.62, p = 0.0001).

Conclusions: With the limitations of any retrospective analysis, the results of this large study may suggest that the addition of MET to EVE and/or SA can provide clinical benefits in advanced diabetic pNET pts. Prospective evaluations are required to confirm these preliminary findings.

Clinical trial identification: Protocol number INT 85/15, approved by Ethical committee of Fondazione IRCCS Istituto tumori Milano on 15 June 2015.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori di Milano

Funding: Fondazione IRCCS Istituto Nazionale Tumori di Milano

Disclosure: S. Pucciddu: Ipsen, Novartis, Italfarmaco, Pfizer. All other authors have declared no conflicts of interest.
Background: NETwork! is a new translational programme purpose-built to conduct deep genomic analysis of NETs within an integrated scientific and clinical practice. Methods: A clinical and ethical framework was established to support, interpret and return genomic analyses, including a clinically-annotated national registry of NETs and a customised bioinformatic platform. Results: pNETs carry relatively few mutations, their genomic landscape dominated by changes in pancreatic NETs were highly tumour-specific, including somatic mutations from recurrent mutations in MEN1 (39%) and ATRX (7%), the driver genomic modifiers as MEN1 (n = 9), EZH2 (n = 6) and HIC1 (n = 5). Variants in genes involving SWI/SNF complex as ARID, BCL-2 and SMARCA have also been found. Regarding the mTOR pathway, several variants were observed in PIK3 family. Methods: Fresh-frozen tumor normal pairs from 35 typical carcinoid (TC), 4 atypical carcinoid (AC) and 9 large-cell neuroendocrine carcinoma (LCNEC) patients were consecutively collected from three European centers (GR, CCML, ICH) between Feb 2010 and Nov 2013. All specimens were reviewed by expert pathologists and those with more than 65% tumor cells on H&E were selected. Genomic DNA (gDNA) was extracted from tumor and matched normal tissue. After normalization and quality control, gDNA was captured using in-solution enrichment methodology (Human All Exon V5 + UTR-V5 75 Mb, Agilent Technologies). Exome enriched libraries were sequenced on an Illumina HiSeq 2000 with a paired-end 2 x 100 bp protocol. Variants were called using VarScan2 against the reference genome hg19 (GRCh37). After filtering based on frequency, variants were annotated using SnpEff and SnpSift with dbSNP and dbNSFP. Results: Fifty-nine percent of TC and AC were females, 89% of LCNEC were males. Median age was 57 (18-85) yrs, 26 (34%) stage I, 16 (24%) stage II, 3 (6%) stage III and 3 (6%) stage IV. On average, 11.6 Gb of sequence were produced per sampling (mean coverage of 72 X). A median of 277 (10-8470) somatic variants per sample was observed. Overall, preliminary analysis showed several somatic variants in histone modifiers as MEN1 (n = 9), EZH2 (n = 6) and HIC1 (n = 5). Variants in genes involving SWI/SNF complex as ARID, BCL-2 and SMARCA have also been found. After excluding the mTOR pathway, several variants were observed in PIK3 family. However, none of the alterations mentioned above were enriched in any subgroup. Nevertheless, TP53 (n = 6) and RB1 (n = 3) variants were observed exclusively in LCNEC. Conclusions: Our preliminary overview of the molecular landscape in pNETs provides the basis for further analysis. The deep analysis of the first 61 patients might potentially represent an actionable target. An exhaustive bioinformatic analysis will be presented. Legal entity responsible for the study: Gustave Roussy Funding: Georges Mathé/ESMO fellowship Disclosure: All authors have declared no conflicts of interest.

Genomic profile in pulmonary neuroendocrine tumors (pNETs): the whole-exome sequencing (WES) as a strategic tool

Methods: A clinical and ethical framework was established to support, interpret and return genomic analyses, including a clinically-annotated national registry of NETs and a customised bioinformatic platform. Results: pNETs carry relatively few mutations, their genomic landscape dominated by changes in pancreatic NETs were highly tumour-specific, including somatic mutations from recurrent mutations in MEN1 (39%) and ATRX (7%), the driver genomic modifiers as MEN1 (n = 9), EZH2 (n = 6) and HIC1 (n = 5). Variants in genes involving SWI/SNF complex as ARID, BCL-2 and SMARCA have also been found. Regarding the mTOR pathway, several variants were observed in PIK3 family. Methods: Fresh-frozen tumor normal pairs from 35 typical carcinoid (TC), 4 atypical carcinoid (AC) and 9 large-cell neuroendocrine carcinoma (LCNEC) patients were consecutively collected from three European centers (GR, CCML, ICH) between Feb 2010 and Nov 2013. All specimens were reviewed by expert pathologists and those with more than 65% tumor cells on H&E were selected. Genomic DNA (gDNA) was extracted from tumor and matched normal tissue. After normalization and quality control, gDNA was captured using in-solution enrichment methodology (Human All Exon V5 + UTR-V5 75 Mb, Agilent Technologies). Exome enriched libraries were sequenced on an Illumina HiSeq 2000 with a paired-end 2 x 100 bp protocol. Variants were called using VarScan2 against the reference genome hg19 (GRCh37). After filtering based on frequency, variants were annotated using SnpEff and SnpSift with dbSNP and dbNSFP. Results: Fifty-nine percent of TC and AC were females, 89% of LCNEC were males. Median age was 57 (18-85) yrs, 26 (34%) stage I, 16 (24%) stage II, 3 (6%) stage III and 3 (6%) stage IV. On average, 11.6 Gb of sequence were produced per sampling (mean coverage of 72 X). A median of 277 (10-8470) somatic variants per sample was observed. Overall, preliminary analysis showed several somatic variants in histone modifiers as MEN1 (n = 9), EZH2 (n = 6) and HIC1 (n = 5). Variants in genes involving SWI/SNF complex as ARID, BCL-2 and SMARCA have also been found. After excluding the mTOR pathway, several variants were observed in PIK3 family. However, none of the alterations mentioned above were enriched in any subgroup. Nevertheless, TP53 (n = 6) and RB1 (n = 3) variants were observed exclusively in LCNEC. Conclusions: Our preliminary overview of the molecular landscape in pNETs provides the basis for further analysis. The deep analysis of the first 61 patients might potentially represent an actionable target. An exhaustive bioinformatic analysis will be presented. Legal entity responsible for the study: Gustave Roussy Funding: Georges Mathé/ESMO fellowship Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology abstracts

Impact of prior therapies on everolimus treatment in the subgroup of patients with advanced lung neuroendocrine tumors (NET) in the RADIANT-4 trial

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Background: Treatment paradigms in lung NET have conventionally relied on therapies such as chemotherapy, radiotherapy and somatostatin analogs (SSA) although evidence from randomized clinical trials remains limited. In the recent subgroup analysis of a large, phase 3, RADIANT-4 study everolimus (EVE), an mTOR inhibitor showed clinically meaningful 6-month improvement in PFS (EVE vs placebo (PBO): 9.2 (6.8-10.9) vs 3.6 (1.9-5.1) mos) and reduced tumor progression risk by 50% (HR: 0.50; 95% CI, 0.28-0.88) in patients with advanced, progressive, nonfunctional lung NET compared to PBO (Fazio et al. 2016 ENETS). This post-hoc analysis evaluates the impact of prior-therapies on EVE treatment in lung NET patients from the RADIANT-4 study.

Methods: Patients with advanced non-functional lung or GI NET were randomized to the EVE arm and 27 patients to the PBO arm. Median age, 65 years; males: 52%; most pts (99%) had well-differentiated disease; Caucasian 86%; WHO PS 0/1/2: 71%/28%/1%. Prior therapies (EVE vs PBO) included: SSA (most for tumor growth control, 43% vs 41%), radiotherapy including peptide receptor radiolucide therapy (PRRT) 40% vs 48%, chemotherapy (40% vs 48%) and no prior therapy (14% vs 11%). Median PFS in the subgroups of patients receiving each of the prior-therapies is listed in the Table. The most common drug-related adverse events (AEs) ≥ 5% incidence in either arm for the whole lung subgroup were stomatitis, rash and fatigue.

<table>
<thead>
<tr>
<th>Prior-therapies</th>
<th>EVE Median PFS, mos (95% CI)</th>
<th>PBO Median PFS, mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>8.5 (3.6,11.7)</td>
<td>2.9 (1.8,3.7)</td>
</tr>
<tr>
<td>Radiotherapy*</td>
<td>9.2 (5.7,NE)</td>
<td>3.0 (1.9,5.1)</td>
</tr>
<tr>
<td>SSA therapy</td>
<td>9.5 (6.0,11.7)</td>
<td>3.7 (1.0,11.2)</td>
</tr>
<tr>
<td>No prior therapy</td>
<td>9.7 (9.9,NE)</td>
<td>3.6 (1.7,NE)</td>
</tr>
</tbody>
</table>

*Includes PRRT

Conclusions: EVE showed PFS benefit in patients with advanced lung NET regardless of prior-therapies, consistently with the overall RADIANT-4 study. No prior-therapy specific safety signal was seen in any of the subgroups.

Table: 421PD

Clinical trial identification: NCT01524793

Legal entity responsible for the study: Novartis Pharmaceuticals

Disclosure: R. Buzzonì: Grants and non-financial support from Novartis, grants from Otsuka, grants and non-financial support from Ialisarmac, non-financial support from Ipsen, during the conduct of the study. J. Strosberg: Grants and personal fees from Novartis, grants from Pfizer, personal fees from Bayer, Genentech, during the conduct of the study; personal fees from Ipsen, Lexicon, outside the submitted work. M. Volì: A. Riddidì, L. Bubuteishvili-Pacaud: Employment - Novartis; F. Herbst: Employment - Novartis, Stock options - Novartis; E. Wolin: Advisory Board - Advanced accelerator applications. N. Fazio: Grants, personal fees and non-financial support from Novartis, personal fees and non-financial support from Ipsen, during the conduct of the study; personal fees from Ialisarmac, Ipsen, Lexicon, outside the submitted work. All other authors have declared no conflicts of interest.

Clinical trial identification: TELESTAR: NCT01677910, primary completion date (march 2016) TELECAST: NCT02063659, primary completion date (march 2016)

Legal entity responsible for the study: Lexicon Pharmaceuticals, Inc.

Funding: Lexicon Pharmaceuticals, Inc.

Conclusions: Integrated safety analyses of placebo-controlled data support the proposed use of TE for the treatment of CS in patients receiving SSA therapy.

Table: 422PD

Annals of Oncology
Disclosures: M. Kulke: Conflict of interest: Consulting for Lexicon Pharmaceuticals; No other relationships/conditions/circumstances that present a potential conflict of interest. Dr Kulke reports other from Lexicon Pharmaceuticals, during the conduct of the study.D. Horsch: Personal fees and other from Lexicon Pharmaceuticals, Inc, grants, personal fees and other from Novartis Pharma, personal fees and other from Ipsen Pharma, personal fees and other from Pfizer Pharma, outside the submitted work.M. Caplin: Personal fees from Lexicon, personal fees from Novartis, personal fees from IPSEN, outside the submitted work.L. Anthony: Grants and personal fees from Lexicon Pharmaceuticals, Inc, during the conduct of the study.E. Grgalov: Other from Lexicon, during the conduct of the study; other from Novartis, other from Ipsen, outside the submitted work.R. Warner: Personal fees from Lexicon, personal fees from Novartis, outside the submitted work.P. Lapierta: Employee of Lexicon Pharmaceuticals during the conduct of the study. I am an employee of Lexicon Pharmaceuticals and have been compensated with salary, stock, and stock options. M. Paliy: Personal fees from Novartis, personal fees from Ipsen, personal fees from Pfizer, outside the submitted work. All other authors have declared no conflicts of interest.

423PD | Phase I, open-label, dose-escalation study of SNX-5422 plus everolimus in neuroendocrine tumors (NETs)


Background: SNX-5422 is an orally bioavailable pro-drug of SNX-2112, a highly effective drug against NETs in preclinical settings. We conducted this Phase 1, open-label, dose-escalation study to determine the maximum tolerated dose (MTD) of SNX-5422 when given with EVR. Secondary objectives were to assess the safety, tolerability, antitumor activity, and pharmacokinetics of SNX-5422 in patients with NETs.

Methods: Patients with NETs were treated with SNX-5422 plus EVR. Dose escalation was performed in 8 cycles. Patients were treated with 28-day cycles of SNX-5422 plus EVR starting at 10 mg daily and increasing in 25 mg increments per cycle up to 150 mg daily plus EVR. In cycle 1, 10 mg was used as the starting dose. The MTD was the dose level where 2 or fewer patients experienced dose-limiting toxicities (DLTs). Cycles 2 and 3 were used to determine the MTD. Toxicities were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Results: In total, 46 patients were enrolled in the study. The median age was 59 years. Most patients (84%) had metastatic disease. Approximately 16% of patients had small bowel NETs, 14% had pancreatic NETs, 28% had rectal NETs, and 48% had lung NETs. The MTD was not established because of one DLT at 100 mg daily plus EVR and two DLTs at 150 mg daily plus EVR.

Conclusions: SNX-5422 plus EVR was well tolerated. The MTD was not established. However, dose escalation is ongoing, and clinical activity is being observed. Additional data regarding safety, pharmacokinetics, and antitumor activity are needed to further assess the potential of SNX-5422 plus EVR for patients with NETs.

424PD | Multicentre evaluation of the role of Gallium DOTA-PET (GaPET) imaging in well differentiated bronchioloalveolar carcinoma (BC): Impact on patients’ (pts) management

A. Lamarca1, D.M. Pritchard2, T. Westwood3, G. Papaxoinis1, S. Vinjamuri4, J. W. Valler5, P. Monohan6, W. Mansoor7

Background: New nuclear medicine imaging techniques have improved diagnosis, staging and treatment planning for BC. GaPET is preferable to standard somatostatin receptor scintigraphy where available (ENETS guidelines), however, its role in the management of BC remains unclear.

Methods: All consecutive pts diagnosed with BC from two ENETS Centres of Excellence were identified retrospectively; pts with high grade tumours or lacking biopsy confirmation were excluded. Primary objective: to assess the impact of GaPET on clinical management in pts with BC.

Results: Of 166 pts screened, 46 were eligible: 52% female, median age 57 years (range 21-86); type of BC: DIPNECH (4%), typical (44%), atypical (35%), not reported (17%); median Ki67 and mitotic count were 3 and 1, respectively; Stage: localised (63%), locally advanced (13%) and metastatic (17%); 27 pts (59%) had curative resection, 18 (39%) received palliative treatment (somatostatin analogue (12), chemotherapy (4), PRRT (1, 3%), debulking surgery (1, 3%). A total of 47 GaPETs were performed with the following rationale: BC confirmation (40%), primary tumour identification (2, 4%), post-surgical assessment (19, 40%), staging (patients with known BC present at time of GaPET) (19, 40%) and consideration of Peptide Receptor Radionucleide

Legal entity responsible for the study: Yolarx Consultants

Funding: Ipsen Pharma

Disclosure: A. Bergamasco. Y. Moride: Affiliated with Yolarx Consultants, which received a grant from IPSEN Pharma to conduct this research project. Dinet, A. Berthon, S. Gabriel, G. Nayroles: Employee of Ipsen Pharma

References:

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A population based analysis of outcome of chemotherapy for metastatic pulmonary large cell neuroendocrine carcinoma: does the regimen matter?

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Background: It is unclear what constitutes optimal chemotherapy for metastatic pulmonary large cell neuroendocrine carcinoma (LCNEC). Expert opinion based guidelines favor platinum-etoposide, i.e. small cell lung cancer (SCLC) type chemotherapy treatment. However, data are lacking due to low incidence of LCNEC and changes in diagnosis after pathology revision. In a population based, pathology revised LCNEC series we compared overall survival (OS) of non-small cell lung carcinoma (NSCLC) and SCLC type chemotherapy treatment.

Methods: Data of the Dutch Pathology Registry (PALGA) and Netherlands Cancer Registry were combined and searched for patients with stage IV definite LCNEC and possible LCNEC treated with chemotherapy, diagnosed between 2003-2012. In 207 patients original tumor specimen slides were available for central revision blinded for clinical information. Data on clinical characteristics, chemotherapy and OS were retrieved. First-line platinum chemotherapy was clustered: 1) NSCLC type treatment including gemcitabine, docetaxel, paclitaxel and vinorelbine, 2) penetrated (P)-NSCLC, and 3) SCLC type treatment including etoposide. Multivariate regression analysis included variables significant at univariate analysis and the variables gender and age.

Results: 128 patients had panel-consensus definite LCNEC. 62% (N = 79) received ≥ 2 cycles of chemotherapy. NSCLC type chemotherapy was administered in 46% (N = 60), Pem-NSCLC in 16% (N = 20), and SCLC type in 38% (N = 48) patients. NSCLC type chemotherapy treated patients had a median OS of 8.5 (95% confidence interval (CI) 7.0-9.9) months, significantly higher than treatment with Pem-NSCLC; median 5.9 [95% CI 5.0-6.9] months ( Hazard Ratio (HR) = 2.51 [95% CI 1.94-3.2], p = 0.002) and SCLC, median 6.7 [95% CI 5.0-8.5] months (HR = 1.66 [1.08-2.56], p = 0.02).

Conclusions: This population based analysis on outcome of chemotherapy in patients with panel-consensus LCNEC shows that NSCLC type chemotherapy treatment leads to prolonged OS when compared to SCLC and Pem-NSCLC type chemotherapy treatment.

Legal entity responsible for the study: Maastricht University Medical Centre

Funding: This study was supported by a grant from the Dutch Cancer Society (KWF: number 7110)

Disclosure: H. Groen: Other: from Lilly, GSK, Merck, Pfizer, Roche, BMS, outside the submitted work, E.J. Speel: Other: from Pfizer, Roche, AstraZeneca, Lilly, MSD, Pfizer, and Amgen, outside the submitted work, A.M.C. Dingemans: Personal fees from Roche, BMS, Boehringer Ingelheim, Astra Zeneca, Eli Lilly, MSD, Pfizer, and Amgen, outside the submitted work; All other authors have declared no conflicts of interest.
Neuroendocrine neoplasms of the appendix including goblet cell carcinoids

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Oncoogy, MSC Memorial Cancer Centre and Institute Maria Skłodowska-Curie, Warsaw, Poland, Endocrinology, Medical University of Gdańsk, Gdańsk, Poland, Surgery, MSC Memorial Cancer Centre and Institute Maria Skłodowska-Curie, Warsaw, Poland

Background: Neuroendocrine neoplasms of the appendix are common GEP-NEN tumours. The aim of this retrospective study was to review patients records with this type of NEN, to determine natural history and outcomes base on localisation of primary tumour, resection margins, initial clinical stage and cell differentiation as single institution experience.

Methods: All patients with confirmed appendiceal NEN, with evaluation of resection margins, localisation of primary tumour and tumour type, based on localisation of regional and distant spread of disease. Also relatively better prognosis in terms of OS in those with rectal and caecal compare to other segments of large bowel NEN. The MANEC variant of colorectal NEC seems to be less aggressive behaviour compare to pure NEC.

Results: A total of 97 pts were included in this study. A female to male ratio was 1.62. There were 79 pts with NETG1 (81%), 7 pts with NETG2 (7%), and 9 in goblet cell carcinoids (GCC) (9%) and 2 pts with MANEC (2%). The resection R0 was in 63 subjects in NETG1 (80%), 4 pts in NETG2 (57%) and 4 subjects with GCC (44%), no one of MANEC pts had R0. Resection R1 was noted in 13 subjects with NETG1 (16%), 2 pts with NETG2 (29%), and 3 pts with GCC (33%). All MANEC pts and 2 pts GCC had R2 resection. The 5 years OS in study group was 95%. There was no difference in 5 years OS between NETG1 and NETG2. There was no significant difference between 5 years OS in pts with R0 98.1% and R1 91%. In group of MANEC and GCC 5 years survival was 85%. The distribution of localisation of primary tumour within appendix presented in table below.

<table>
<thead>
<tr>
<th>Classification</th>
<th>ALL</th>
<th>NETG1</th>
<th>NETG2</th>
<th>MANEC</th>
<th>GCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top</td>
<td>73 (75%)</td>
<td>65 (67%)</td>
<td>6 (6%)</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Middle</td>
<td>11 (11%)</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Base</td>
<td>9 (9%)</td>
<td>7 (7%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>No-data</td>
<td>3 (3%)</td>
<td>3 (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions: Appendiceal NEN had very favourable prognosis. Most of them are treated completely surgical. Even R1 resection had no significant impact on 5 years survival. Over 90% of cases are well or moderately differentiated. MANEC and GCC are very rare and represent less than 10% of all cases.

Legal entity responsible for the study: Lukasz Jaskiewicz, Jaroslaw Cwikla, University of Warmia and Mazury in Olsztyn, Faculty of Medical Sciences, Department of Radiology

Disclosure: All authors have declared no conflicts of interest.
Background: Neuroendocrine tumors (NETs) are the most common appendiceal tumors and can be categorized as well-differentiated NETs (WDNETs) and mixed adenoneuroendocrine tumors (MANECs). Currently, WDNETs are classified based on the American Joint Committee on Cancer (AJCC) staging (seventh edition), first proposed in 2010 or according to the European Neuroendocrine Tumor Society staging systems (ENETS). Both systems differ slightly in the T stage. MANECs, which are more aggressive, are staged according to AJCC staging for appendiceal adenocarcinomas. However, the prognostic value of AJCC staging in WDNETs and MANECs has not been validated.

Methods: Patients (pts) diagnosed with appendiceal WDNET and MANEC (between 1988-2012) in the Surveillance, Epidemiology and End Results (SEER) program were assigned stages I-V according ENETS (WDNETs only) or AJCC 7th edition (WDNETs and MANECs). Kaplan-Meier method and univariate Cox model were used to estimate overall survival (OS) and differences in OS across stages, respectively.

Results: We identified 860 and 1173 pts with WDNET and MANEC, respectively. The 10-year survival rates for WDNETs according to ENETS stages I-V were 96%, 95%, 92%, and 55%, respectively (P < 0.001, log rank). The corresponding rates for AJCC stages I-V were 95%, 94%, 90%, and 53%, respectively (P < 0.001, log rank). Using univariate cox regression for WDNETs, only stage IV was associated with poor survival in both ENETS and AJCC (per ENET: HR = 8.27, 95%Ci = 3.72-18.35, p < 0.001 and per AJCC: HR > 9.7, 95%Ci = 5.11-17.18, p < 0.001). The agreement between AJCC and ENETs per weighted Cohen’s kappa coefficient was estimated to be 0.73 (95% CI = 0.70-0.76), indicating substantial agreement and moderate discrepancy. For MANEC, the number of pts with stage I-IV was 230 (19.61%), 625 (53.28%), 176 (15.26%) and 139 (11.85%) respectively. By AJCC staging, median OS was 52 months, 43 months, 28 months and 17 months for stage I-IV, respectively (P < 0.001, log rank). The corresponding rates for AJCC stages I-IV were 96%, 95%, 93%, and 55%, respectively (P < 0.001, log rank). The corresponding rates for AJCC stages I-IV were 92%, and 55%, respectively (P < 0.001, log rank). The corresponding rates for AJCC stages I-IV were 92%, and 55%, respectively (P < 0.001, log rank). The corresponding rates for AJCC stages I-IV were 92%, and 55%, respectively (P < 0.001, log rank).

Conclusions: ENETS staging system in neuroendocrine tumors appears to be a more robust approach than AJCC, but both systems need to be improved. Further analysis is currently in progress in a larger group of NET patients. Investigation of EZH2 inhibitor drugs in pNET appears feasible.

Legal entity responsible for the study: Azienda Ospedaliera Universitaria Pisana

Funding: Fondazione Aprio

Disclosure: All authors have declared no conflicts of interest.

Enhancer of zeste homolog 2 (EZH2) expression in well and moderately differentiated pancreatic neuroendocrine tumours (pNET)

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Background: Enhancer of zest homolog 2 (EZH2) expression in well and moderately differentiated pancreatic neuroendocrine tumours (pNET) is correlated to overall survival (OS) and disease-free survival (DFS) in patients with pNET. EZH2 is the catalytic subunit of polycomb repressive complex 2 with histone H3 methyltransferase function. EZH2 has been shown to be over-expressed in several malignant neoplasms and to be associated with aggressive behaviour. Few data are currently available for NETs. EZH2 represents a potential therapeutic target and EZH2 inhibitor drugs are in development. In this study, we evaluated EZH2 expression in well differentiated G1 (Ki67 <2%) or moderately differentiated G2 (2% < Ki67 <20%) pNET to investigate any correlations with histological and clinical parameters.

Methods: Immunohistochemical analyses for nuclear EZH2 expression were performed on a consecutive series of 218 pNET (118 G1, 100 G2). Immunohistochemical analysis was performed using the rabbit monoclonal antibody against EZH2 and Expression of EZH2 was assessed by an independent pathologist. 

Results: Three patients with pNET have been assessed (9 G1 and 21 G2 pNET). Eleven patients had metastatic tumors at median time of 49 (15-114) months, 8 patients had synchronous metastases and 11 patients had primary tumor radically removed without recurrence of disease. EZH2 was overexpressed in both G1 and G2 pNET. We found no significant difference of EZH2 expression between G1 and G2 pNET. In metastatic patients, negative score (<10%) was documented in 87.5% of metastatic metastatic patients and in 18.2% of synchronous metastatic patients (p <0.001).

Conclusions: EZH2 is expressed in pNET. Data show a statistically significant difference in the expression of EZH2 between groups with metachronous metastases (more indolent clinical course), and the group with synchronous metastases (more aggressive clinical course), with lower expression in the first group. This data could be interesting in terms of therapeutic strategy. Further analysis are currently in progress in a larger group of NET patients. Investigation of EZH2 inhibitor drugs in pNET appear feasible.

Legal entity responsible for the study: Azienda Ospedaliera Universitaria Pisana

Funding: Fondazione Aprio

Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology
Reassessment of proliferative activity at disease progression in neuroendocrine neoplasms

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Background: The proliferative index Ki-67 is a key prognostic factor influencing prognosis and therapeutic approach in NENs. However, the role of histological reassessment at time of progression of disease (PD) is still debated. The aim was to investigate Ki-67 modifications at time of PD in NENs.

Methods: Analysis of sporadic NENs in which histology was repeated at time of PD. Values are expressed as median (range), and compared by Wilcoxon test.

Results: 48 pts, median age 56 (23-74 yr), were included. Among these, at time of PD, 33.4% (16 pts) had recurrent disease after previous radical surgery, and 66.6% (32 pts) showed increase in lesions number/size. Primary tumour were prevalent pancreas (52%, 25 pts) and distal jejunum/ileum (33.4%, 16 pts). At time of initial evaluation, 47.9% of pts (n = 23) had G1 tumour, whereas 52.1% (n = 25) had G2 tumour. Median Ki-67 was 3% (1%-20%). The median interval between initial assessment and repeated histology was 54 months (2-148). During this period, patients received the following treatments: somatostatin analogs (52%, 25 pts), PRRT (25%, 12 pts), systemic chemotherapy (10.4%, 5 pts), everolimus (14.6%, 7 pts). At time of PD, 64.6% of pts (n = 31) showed increase in Ki-67 (21 pancreas, 8 distal jejunum/ileum, 2 other primary NENs). A G1 grading step-up was observed in 15 pts (11 pNENs; 4 non-pNENs): 11 pts changed from G1 to G2, 4 pts from G2 to G3. Overall, median Ki-67 increased to 7.5% (range 1%-70%; P = 0.003 vs Ki-67 at time of initial assessment). Specifically, Ki-67 significantly changed in pNENs from a median value of 2% to 5% (p = 0.32). As far as the kind of PD is concerned, no difference in terms of Ki-67 change was observed between patients who underwent disease recurrence after radical surgery and those who underwent disease recurrence after radical surgery.

Conclusions: Ki-67 increase occurred in 64.6% of NENs at time of PD. A statistically significant modification was observed in pNENs. Reassessment of proliferative activity at time of progression should be considered, especially in pNENs. This information might help physicians to plan proper patients’ management.

Legal entity responsible for the study: Sapienza’ University of Rome

Disclosure: All authors have declared no conflicts of interest.
Efficacy of lanreotide autogel/depot (LAN) vs placebo (PBO) for symptomatic control of carcinoid syndrome (CS) in neuroendocrine tumor (NET) patients from the ELECT study


Background: In the 16-week double-blind (DB) phase of ELECT, LAN significantly reduced the need for short-acting octreotide (OCT) rescue medication for symptomatic control of CS in NET patients vs PBO (primary result). We present posthoc data on patient-reported symptoms during DB treatment.

Methods: ELECT consisted of a 16-week DB, 32-week initial open-label, and long-term phases. Adults with histopathologically confirmed NET and history of CS (diarrhea and/or flushing) were randomized to LAN 120 mg every 4 weeks. Patients could administer short-acting OCT if needed and were instructed to record daily the frequency and severity of symptoms in a diary using Interactive Voice (Web) Response System for 1 month pre-randomization and throughout the DB phase. Analysis of covariance (ANCOVA) was used for these analyses with baseline symptoms, prior SSA, and country as factors. Given the high variability of urinary 5-hydroxyindoleacetic acid (SHIAA), values were log transformed.

Results: 115 patients were randomized (n = 59 LAN, n = 56 PBO). In the DB phase, percentages of days with severe or moderate/severe diarrhea and/or flushing compared to baseline were significantly reduced for LAN vs PBO (Table). The LAN group had a 33% greater decrease in logarithmic SHIAA levels at wk 12 vs PBO (relative mean 0.65; 95% CI: 0.40, 1.07). Treatment-emergent adverse events occurred in 53.4% of patients on LAN and 59.6% of patients on PBO.

Table: Percentages of days with severe or moderate/severe diarrhea and/or flushing compared to baseline were significantly reduced for LAN vs PBO (Table).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (%)</th>
<th>LS Mean (SE)</th>
<th>% reduction</th>
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<tr>
<td>LAN (n = 59)</td>
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<td>23.4 (3.06)</td>
<td>33%</td>
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<tr>
<td>PBO (n = 56)</td>
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<td>26.4 (3.12)</td>
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<tr>
<td>LAN vs PBO (95% CI)</td>
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<td>-3.0 (-5.2, -0.8)</td>
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</tr>
</tbody>
</table>

Conclusions: The observed improvement in patient-reported symptoms supports the efficacy of LAN in CS. These findings are in concert with the previously reported primary result of less rescue medication use with LAN vs PBO.

Clinical trial identification: EudraCT 2010-019066-92, NCT00774930 authors: on behalf of ELECT study investigators

Legal entity responsible for the study: Ipsen Biopharmaceuticals, Inc.

Funding: The study was funded by Ipsen Biopharmaceuticals, Inc.

Disclosure: E.M. Wolin: Consulting or Advisory Role - Celgene, Ipsen, Novartis; Pfizer, Research Funding – Ipsen (Inst), Novartis (Inst), Pfizer (Inst). G.A. Fisher, P.L. Kurz: Research funding from Genentech, Merck, Advanced Accelerator Applications, Lexicon, OxiGene. A. Vinik: Research funding from Ipsen, Novartis N. Liyanage, S.P. Lowenthal, S. Mirakhur: Employment Ipsen Biopharmaceuticals, Inc. A. Vinik: Consulting or Advisory Role – Lias Pharmaceuticals, Merck Co., Inc.; Neumemetric, PamLab, Pfizer; Speakers’ Bureau – Merck Co., Inc., PamLab, Research Funding – Daichichi Sanyo, Impeto Medical, Intarcia Therapeutics; Pfizer; Tericia, Viromed. All other authors have declared no conflicts of interest.

Long-term safety/tolerability of lanreotide autogel/depot (LAN) treatment for metastatic intestinal and pancreatic neuroendocrine tumours (NETs): Final results of the CLARINET open-label extension (OLE)


Background: CLARINET is a landmark study that established the antitumour activity of LAN in patients with metastatic intestinal or pancreatic NETs. Here, we report final long-term safety data from the recently completed OLE.

Methods: Patients were eligible to take part in the OLE if they had stable disease (with LAN or placebo [PBO]) at the end of, or progressive disease (PBO group only), during the 96-week double-blind core study. All patients received open-label LAN 120 mg by deep subcutaneous injection every 4 weeks.

Results: In total, 89 patients were treated over the core and OLE studies (42 continued on LAN in both studies [LAN-LAN group] and 47 switched from placebo to core to LAN in OLE [PROLAN group]). The adverse event (AE) profile of LAN treatment during both studies is summarised in the Table. The most common class of AEs on LAN across both studies was GI events (any AE, 81%; any treatment-related AE [TRAЕ], 43%); among these, the most frequent were diarrhoea (any AE, 40%; any TRAE, 31%) and abdominal pain (any AE, 38%; any TRAE, 17%). On PROLAN in the OLE study, GI events (any AE/any TRAE) occurred in 66%/36%, with diarrhoea in 32%/36% and abdominal pain in 21%/25%. Only five patients withdrew due to AEs, of which only one was treatment-related. No new safety concerns were identified.

Table: AE profile on LAN during the CLARINET core and OLE studies

<table>
<thead>
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<th>Treatment</th>
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<th>LS Mean (SE)</th>
<th>% reduction</th>
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<td>LAN group (n = 42)</td>
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<td>23.4 (3.06)</td>
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<td>PBO group (n = 47)</td>
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<td>LAN vs PBO (95% CI)</td>
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<td>-3.0 (-5.2, -0.8)</td>
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</table>

Conclusions: LAN 120 mg treatment, over a period of up to >4 years, showed favourable safety/tolerability in patients with metastatic intestinal and pancreatic NETs. This supports the positive longer-term benefit-risk profile of LAN as an antitumour treatment, which is consistent with previous experience from shorter-term trials.

Clinical trial identification: 2-55-52030-728

Legal entity responsible for the study: N/A

Funding: Ipsen

Disclosure: M. Caplin: Received consulting/advisory fees from Ipsen. M. Pavei: Received research funding from Novartis and consulting/advisory fees from Ipsen, Novartis, Pfizer and Lexicon. J.C. Cvikla: Received research funding from Ipsen. A. Phan: Received research funding from Ipsen, Novartis, Lexicon, Sanofi and Incyte; consulting/advisory fees from Ipsen and Novartis; and speaker fees from Lilly, Genentech, Celgene, Novartis and Ipsen. R. Adler: Received research funding from Novartis, Ipsen, Roche, Pfizer, Bayer and Celgene, and speaker fees from Novartis, Ipsen, Roche, Pfizer and Celgene. G. Cikrtil: Received research funding from Ipsen and consulting/advisory fees from Ipsen, Novartis, Keycey. E. Wolin: Received...
research funding from Ipsen and Novartis; consulting/advisory fees from Ipsen, Novartis, Pfizer and Celgene; and honoraria from Ipsen and Novartis.} Capdevila: Received consulting/advisory fees from Ipsen, Novartis, Pfizer. G. Rindi: Has received speaker fees from Ipsen, N. Liyanage, S. Braun: Employee of Ipsen. P. Ruszniewski: Received research funding from Ipsen and Novartis, speaker fees from Ipsen and Novartis, consulting/advisory fees from Ipsen, honoraria from Ipsen and Novartis. All other authors have declared no conflicts of interest.

**Background:** In ELECT, LAN significantly reduced the need for short-acting octreotide rescue medication for symptomatic control of CS in NET patients vs placebo (PBO) in the 16-wk double-blind (DB) phase (primary result). Here we compare patient-reported symptoms in the DB vs 32-wk initial open-label phase (IOL).

**Methods:** Adults with histologically confirmed NET and history of CS with/without prior somatostatin analog (SSA) use were randomized to DB LAN 120 mg or PBO every 4 wks for 16 wks followed by a 32-wk IOL on LAN. Patients reported daily the frequency and severity of diarrhea and/or flushing by Interactive Voice (Web) Response System for 1 month pre-randomization through IOL. Mean composite symptom scores (frequency x severity) in DB vs IOL were analyzed posthoc. Analysis of covariance models (ANCOVA) were used for these analyses with baseline symptoms, prior SSA, and country as factors.

**Results:** Of 115 randomized (n = 59, LAN; n = 56, PBO); 56 LAN- and 45 PBO-treated patients, switched to LAN, were available for IOL analysis. Among patients initially on LAN, composite diarrhea scores improved significantly from DB to IOL (mean difference 0.7, 95% CI 0.22, 1.20; p = 0.005) and were significantly different for flushing (mean difference -0.2, 95% CI -1.25, 0.80) or diarrhea and flushing (mean difference 0.5, 95% CI -0.69, 1.67). As expected, the mean difference in composite scores for diarrhea (1.1, 95% CI 0.49, 1.63), flushing (1.1, 95% CI 0.19, 1.93), and diarrhea / flushing (2.1, 95% CI 0.91, 3.35) reflected significant improvement from DB to IOL for patients initially on P (P-values <0.05). Mean (95% CI) differences in uSHIAA between DB wk 12 and IOL wk 44 were -14.75 µmol/d (27.02, 56.51) for LAN (DB) – LAN (IOL) and 73.96 µmol/d (11.77, 159.7) for PBO (DB) – LAN (IOL). Frequency of treatment-emergent adverse events (AEs) during IOL by DB group (LAN, PBO) was 69.6% vs 71.1%. The AE profile during IOL was similar to DB.

**Conclusions:** Improved control of diarrhea and flushing in CS patients during initial 16 wks of LAN was sustained through wk 48 of this phase 3 study. Here we compare patient-reported symptoms in the DB vs 32-wk initial open-label phase (IOL).

**Legal entity responsible for the study:** George A. Fisher, Jr.

**Funding:** This study was funded by Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA.

**Disclosure:** G.A. Fisher Jr: Consulting—Ipsen; Research Funding—Ipsen, E. Wotin; Consulting or Advisory Role—Celgene; Ipsen, Novartis, Pfizer; Research Funding—Ipsen (Inst), Novartis (Inst). Pfizer (Inst). P.L. Kunz: Research funding from Genentech, Merck, Advanced Accelerator Applications, Lexicon, Oxigene; Advisor for Ipsen; Novartis, N. Liyanage, B. Mirshahi, S. Pitman Lowenthal. Employee Ipsen, Biopharmaceuticals, Inc. A. Vinik: Consulting or Advisory Role—Ilsie Pharmaatronics; Merck Co., Inc.; Neumetrix; Lamblia, Pfizer; Speakers Bureau—Merck Co., Inc.; Pamlab, Research Funding—Daichi Sankyo, Impeck Medical, Intarcia Therapeutics, Pfizer, Terccia, ViroMed. All other authors have declared no conflicts of interest.

**Role of somatostatin analogs (SSA) in combination with targeted agents (TTA) for neuroendocrine tumors (NET) systemic review**

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**Background:** SSA are an accepted antimonial treatment for well-differentiated, G1-2 NETs disregarding site of origin and/or functional status. The effect of the combination of SSA and TTA may be higher than any of its components, as some small retrospective studies have suggested. We aim to determine how that question has been prospectively designed and done in the clinical research field.

**Methods:** We searched MEDLINE and relevant meetings looking for randomized Fz-3 studies and abstracts about testing combinations of SSA (octreotide, lanreotide, pasireotide) and TTA (sunitinib, everolimus, bevacizumab) both formal and unplanned combinations were collected in relation to four aspects: Site of tumour (carcinoid (heu) and non-pancreatic/pancreatic) and functional status (yes/no) For carcinoids the expected appropriate combination would seem to be SSA vs SSA + TTA ("A"), while for pancreatic NETs it should be most probably TTA vs TTA + SSA ("B") An additional search for not published trials was also performed.

**Results:** With respect to comparison "A" only in one study all patients received formal planned SSA-Octreotide, but it was mainly for functional-symptomatic tumors. No published studies in non-functional non-pancreatic NETs approached the "A" comparison. Ongoing trials in carcinoid tumors are better designed to answer the question but they are only testing lanreotide and pasireotide, not octreotide. No trial have tested Bevacizumab + octreotide against octreotide (or other SSA) alone in carcinoid tumors. Otherwise, for comparison "B" in pNETs, two studies analyze everolimus vs everolimus + pasireotide (negative trial), and everolimus + pasireotide (as control arm) plus/minus bevacizumab (with promising results favoring the addition of bevacizumab)

**Conclusions:** Until now more emphasis have been done in the TTA value of the combination than on the potential antimonial activity and synergy of the SSA. Because of the relative rarity of these tumors it is reasonable to choose, within the hierarchic options, those most pragmatic. However it is the paramount importance to design strategic studies as a proof of concept

**Legal entity responsible for the study:** N/A

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.
Prognostic impact of the cumulative dose and dose intensity of everolimus in patients with pancreatic neuroendocrine tumors (PNETs)

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Background: Pancreatic neuroendocrine tumors (PNETs) are still considered a rare disease, which accounts for approximately 10% of all cases of pancreatic cancer. The oral mTOR inhibitor everolimus has become an established standard therapy for patients with advanced PNETs. Aim of the study is to assess if cumulative dose (CD) and dose intensity (DI) of everolimus may affect survival of advanced PNETs' patients.

Methods: One hundred and sixteen patients (62 males and 54 females, median age 55 years) with advanced PNETs were treated with everolimus for at least 3000 mg despite delays or temporary interruptions. Patients were stratified into two groups, with CD ≤ 3000 mg (Group A; n = 68) and CD > 3000 mg (Group B; n = 48).

Results: The response rate and toxicity were comparable in the two groups. However, patients in group A experienced more dose modifications than patients in group B. Median OS was 24 months in Group A whilst in Group B it was not reached (HR: 2.6; 95% CI: 1.10-7.67; p < 0.0001). Patients who maintained a DI higher than 9 mg/day experienced a significantly longer OS and experienced a trend to higher response rate.

Conclusions: Overall, our study results showed that both CD and DI of everolimus may affect survival of advanced PNETs' patients. Furthermore, everolimus and sunitinib were well tolerable and effective in patients with advanced non-functioning gastrointestinal neuroendocrine tumors (GI-NETs): EVERLAR study

J. Capdevila1, A. Teruel1, J. Barrués2, D. Castellano3, C. Lopez2, J.L. Manzano3, V. Aixela4, R. Garcia-Carbonero5, E. Dotti6, I. Matos7, A. Custodio8, G. Delle Fave8, N. Fazio8, F.G. De Braud9, M. Falcioni9

1Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain, 2Medical Oncology, Institut Català d’Oncologia Hospital Duran i Reynals, Barcelona, Spain, 3Medical Oncology, Hospital Universitario La Paz, Madrid, Spain, 4Medical Oncology, Hospital Universitat de Deusto, Donostia, Spain, 5Medical Oncology, Hospital Universitario Marqués de Valdecilla, Santander, Spain, 6Medical Oncology, Instituto Oncológico de Oviedo (IOO), Oviedo, Spain, 7Hospital General y Mental and NEURO, Instituto Europeo de Oncología, Milano, Italy, 8Division of Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, 9Medical Oncology, Azienda Ospedaliero - Università Politecnico di Modena, Modena, Italy

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Conclusions: Overall, our study results showed that both CD and DI of everolimus may affect survival of advanced PNETs' patients. Furthermore, everolimus and sunitinib were well tolerable and effective in patients with advanced non-functioning gastrointestinal neuroendocrine tumors (GI-NETs): EVERLAR study

Discussion: All authors have declared no conflicts of interest.

Efficacy and safety of targeted agents for treatment of gastroenteropancreatic (GEP) neuroendocrine tumor (NET)


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Background: Efficacy and safety of targeted agents, such as everolimus and sunitinib, have been demonstrated in the prospective trials for patients with GEP-NET. Considering heterogeneous clinical features of NET, evaluation of real-world outcomes with these agents are necessary. We retrospectively analyze the treatment outcomes of everolimus and sunitinib for patients (pts) with GEP-NET.

Methods: Between Mar 2007 and Oct 2014, a total of 44 GEP-NET pts treated with everolimus or sunitinib were included. Considering distinct characteristics between pancreatic (Pan) and non-PanNETs, efficacy analysis was performed separately, while safety analysis included all pts.

Results: PanNET was most common type (n = 28, 64%) followed by hindgut NET (n = 11, 25%) and foregut NET (n = 5, 11%). Sunitinib and everolimus were given in 27 (61%) and 17 (39%) pts, respectively. Among 41 pts that pathology review was available, tumor grade (G) was GI2 in 36 (78%) and G3 in 5 (12%). Cytotoxic chemotherapy and somatostatin analogue were previously given in 16 (36%) and 18 (41%) pts, respectively. In pts with PanNET, median progression-free survival (PFS) with everolimus and sunitinib was 16.6 months (95% CI, 8.0-25.1) and 8.0 months (95% CI, 0.0-17.4), and there was no significant difference between two agents (p = 0.51). For non-PanNET pts, median PFS was 14.7 months (95% CI, 2.4-27.0) with everolimus and 1.7 months (95% CI, 0.5-3.0; p < 0.001) with sunitinib; G3 tumor and prior cytotoxic chemotherapy were more common in pts with sunitinib than those with everolimus (30% vs 0%, and 76% vs 50%, respectively). Treatment was discontinued due to the adverse events in 3 pts (14%) with sunitinib and 4 (29%) with everolimus. Most common grade 3-4 toxicities were neutropenia (n = 9, 33%), anemia (5, 19%), diarrhea (3, 11%), and hand-foot syndrome (2, 7%) in pts with sunitinib (n = 27), and pneumonitis (2, 12%), and thrombocytopenia/thrombosis (1, 6%) in those with everolimus (n = 17). Tumor grade was a significant predictive factor for PFS (G1/2: median 14.7 months vs G3: 2.5 months, p = 0.002).

Conclusions: Both everolimus and sunitinib were well tolerable and effective in GEP-NET pts. The activity of everolimus was seen across all GEP-NETs and consistent with previous trials.

Legal entity responsible for the study: Asan Medical Center (AMC) IRB

Disclosure: None

Disclosures: All authors have declared no conflicts of interest.
Caperitabine and streptozocin cisplatin for gastrointestinal neuroendocrine tumours: predictors of long-term survival in the NET01 trial

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Background: Cytotoxonic chemotherapy for advanced, unresectable pancreatic and gastrointestinal foregut neuroendocrine tumours (GEPNETs) commonly comprises 5-fluorouracil (5-FU) plus streptozocin (STZ). The NET01 trial, conducted in the pre-inhibitor era, recruited a broad spectrum of patients (pts) to investigate whether capesitabine (Cap) was an acceptable alternative to FU, with or without adding cisplatin (Cis). At median follow up 3-4 years, objective responses (primary endpoint) were reported as similar in the 2 arms, but CapScis was more toxic. Final results are now reported with longer follow up.

Methods: Of 86 (44 CapS, 42 CapScis) pts randomised, 16% had poorly differentiated tumours, although numbers are small. Progression-free survival (PFS) and overall survival (OS) (secondary endpoints) as well as outcome predictors are now reported with longer follow up.

Results: Of 86 (44 CapS, 42 CapScis) pts randomised, 16% had poorly differentiated histology. With long-term median follow-up of 8 years, 83 (97%) pts have progressed/ died and 60 (80%) pts have died. The estimated median PFS was 11.1 months for CapS and 9.6 months for CapScis (HR = 0.82, 95%CI: 0.53, 1.27). Median OS was 27 and 5.6 months for CapS and CapScis (HR = 0.8, 95%CI: 0.53, 1.23) respectively. Median OS was 27 months for CapS and 26 months for CapScis. Median OS was 25.2 (7.0-72.2+ months) respectively. In P-NET median PFS was 7.3 (2.1-72.2+ months): in particular G1 P-NET and G2 P-NET mPFS was 7.5 (2.0-72.2+ months) and 6.1 (2.5-34.0+ months) respectively. In L-NET median PFS was 5.4 (1.4-6.6 months), in U NET it was 2.3 (1.0-16.6) months. At a median follow-up of 40 months, median OS was 48.7 (24.8-85.1+ months). Reported G1-G2 toxicities were diarrhoea, nausea, asthenia, G3-G4 toxicities were not reported.

Conclusions: PFS and OS were similar for the CapS+ Cis regimen. High patient age, tumour Ki67 and grade all predicted for poorer outcomes.

Disclosure: J.W. Valle: Kevcoy (honorary for Advisory Board in 2010 and 2012) - this relates to streptozocin.D. Cunningham: Research funding only to RHM from Amgen, AstraZeneca, Bayer, Celgene, Medimmune, Merrimack, Merck Sero, Sanofi. All other authors have declared no conflicts of interest.

Table: 446P

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</table>

Efficacy of amrubicin monotherapy after platinum chemotherapy for non-gastrointestinal extrapulmonary neuroendocrine carcinoma

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Background: NEC rarely arises in extra-pulmonary sites. Although chemotherapeutic regimens for small cell lung cancer (SCLC) are empirically administrated for unresectable extra-pulmonary NET, the 2nd line treatment is not investigational. We review our experience in metastatic WDNET patients (pts) treated with CapS+ SSA, using pretreated pemetrexed as a standard of care.

Methods: From October 2005, 20 WDNET pts with progressive disease after failure of SSA and/or Everolimus, PRRT, other Chemotherapy, were treated with CapS+ SSA. The primary tumours site was pancreas (P) in 17 pts, intestine (I) in 13 pts, lung (L) in 6 pts, and unknown (U) in 1 pt. Pts received Cap 1600 mg/m2 on days 1-4 and SSA (octreotide LAR 30mg 1 im q8w or lanreotide LAR 120mg 1 im q8w). Treatment efficacy was evaluated by response rate according to RECIST criteria and in terms of Progression Free Survival (PFS). Safety and tolerability were evaluated following CTCAEv4 criteria.

Results: Seventeen pt (80.9%) had a Partial Response, 17 pt (42.9%) showed Stable Disease, 16 (40%) pts showed Progressive Disease, median PFS was 6.1 (1-72.2+) months, 3 pts are still on treatment. In L-NET median PFS was 25.3 (2.2-70.8+) months: in particular G1 L-NET and G2 L-NET mPFS was 46.2 (13.5-70.8+) months and 4.3 (2.2-5.5+) months respectively. In P-NET median PFS was 7.3 (2.0-72.2+) months: in particular G1 P-NET and G2 P-NET mPFS was 7.5 (2.0-72.2+) months and 6.1 (2.5-34.0+) months respectively. In L-NET median PFS was 5.4 (1.4-6.6 months), in U NET it was 2.3 (1.0-16.6) months. At a median follow-up of 40 months, median OS was 48.7 (24.8-85.1+ months). Reported G1-G2 toxicities were diarrhoea, nausea, asthenia, G3-G4 toxicities were not reported.

Conclusions: Pts with CapS+ SSA showed interesting activity and efficacy in pretreated pt with progressive WDNET with acceptable toxicity. In particular, G1 L-NET pts showed partial prolonged mPFS and in this group Cap+ SSA seems a valid therapeutic option.

Disclosure: All authors have declared no conflicts of interest.
Disclosure: Y. Takiguchi: I received lecture fee by Nipponkayaku. All other authors have declared no conflicts of interest.

Safelty and efficacy of lanreotide autogel/depot (LAN) every 14 days for patients with pancreatic or midgut neuroendocrine tumours (NETs) progressing on LAN every 28 days: The prospective, international CLARINET FORTE study

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Background: The CLARINET study demonstrated the antitumor effect of lanreotide autogel (LAN) vs placebo in patients with metastatic gastroenteropancreatic neuroendocrine tumours (NETs) and reaffirmed its favourable safety profile. Patients with progressive disease (PD) receiving LAN 120 mg every 28 days (standard dosing interval) are usually offered aggressive treatments (chemotherapy, targeted therapies, or peptide receptor radionuclide therapy). The CLARINET FORTE study will investigate the safety and antitumor efficacy of a reduced dosing interval (every 14 days) of LAN 120 mg in patients with pancreatic or midgut NETs, beyond progression on the standard dosing interval.

Trial design: CLARINET FORTE is an international, multicentre, prospective, open label phase II study. Main eligibility criteria: adult patients with well-differentiated, metastatic or locally advanced, unresectable, functioning or non-functioning, GI/G2, pancreatic NETs (pNETs) or midgut NETs. Patients will have radiological PD, within 24 months prior to enrolment, as assessed by an independent central review according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.0, while receiving first line treatment with LAN 120 mg on standard dosing interval (ICOG PS 0-2). It is planned to enrol a total of 100 patients, 50 per cohort (pNETs or midgut NETs) in a total of 30–35 sites in Europe and the USA. LAN will be administered by deep subcutaneous injection at a dose of 120 mg every 14 days up to 48 weeks or 96 weeks for the pNET or midgut NET cohorts, respectively, or until PD/ death or early withdrawal due to unacceptable toxicity/tolerability. The primary endpoint is progression-free survival (PFS), based on central review according to RECIST v1.1. Secondary endpoints include overall survival, objective radiologic response rate, effect on symptoms, quality of life, LAN pharmacokinetics, and safety. Analyses will be descriptive and p-values will be provided only for exploratory purposes. As of May 16th, 5 patients were enrolled in the study.

Clinical trial identification: EudraCT 2014-005667-24; ClinicalTrials.gov NCT02651987.

Legal entity responsible for the study: Ipsen

Funding: Ipsen

Disclosure: M. Pavell: Research funding from Novartis. Consulting/advisory fees from Ipsen, Novartis, Pfizer and Lexicon. C. Dromain: Consulting/advisory fees from Ipsen. C. Massien, A. Hourchard: Employee of Ipsen.

Safety of lanreotide 120 mg ATG in combination with metformin in patients with advanced well differentiated gastrointestinal (GI) or lung carcinoids. A piloc, one-arm, open-label, prospective study: The MetNET-2 trial

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Background: In the CLARINET trial, lanreotide (LAN) 120 mg resulted in a 53% reduction in the risk of death or disease progression, compared with placebo, in GI-NET patients. Several studies have identified diabetic patients (pts) as having increased risk for the development of cancer and have associated metformin (MET) treatment with a decrease of cancer risk. MET may have anti-proliferative activity due to its ability to decrease insulin and IGFI levels; in addition, it promotes AMPK activation and TSC1-2/AKT/P13K/AKT/GSK3β. This study evaluates the safety of LAN 120 mg in combination with MET in pts with advanced well-differentiated GI or lung carcinoids.

Trial design: Methods: Pts with advanced GI or lung carcinoids will receive a combination of LAN 120 mg/month and MET 2550 mg/day, until progression or unacceptable toxicity. Radiological progression will be assessed every 4 months. The primary objective is to evaluate the incidence of adverse events (AEs) and severe AEs (SAEs). A 1-stage Herd design will be used. The null hypothesis that the SAEs rate related to the treatment is ≥25% will be tested against a one-sided alternative. 20 pts with available tissue specimens will be enrolled. The null hypothesis will be rejected if ≤2 pts will experience a severe toxicity. This design yields a type I error rate of 10% and power of 85% when the true toxicity rate is 25%. The expression of 111 genes potentially involved in the pathways related to MET (e.g., LKB1, TP53, KRAS, IGFIR, VEGFR, PDGFR, AKT, PI3KCA, PTEN, mTOR) will be assessed by a target NGS approach. Other endpoints include TTP and RR. Results: In March 2016, the trial received institutional ethic board approval and in April 2016 the enrollment was started (EudraCT 2015-004626-34). Recruitment will be completed in April 2017. Conclusions: This study will investigate the safety of the combination of LAN 120 mg and MET and the correlation between tumor mutations and response to this therapy.

Clinical trial identification: Protocol EUDRACT Number: 2015-004626-34 approved by Ethical committee of Fondazione IRCCS Istituto Tumori Milan on 8 March 2016

Legal entity responsible for the study: Fondazione IRCCS Istituto Tumori Milan

Funding: Fondazione IRCCS Istituto Tumori Milan

Disclosure: S. Pusceddu: Ipsen, Novartis, Italfarmaco, Pfizer. All other authors have declared no conflicts of interest.
gastrointestinal tumours, colorectal

Results of a prospective randomised control 6 vs 12 trial: Is greater tumour downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy?

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Background: The optimum interval between CRT and surgery for locally advanced rectal cancer remains controversial. If greater downstaging occurs with a longer interval to surgery, this may impact on rates of sphincter preservation and survival. A prospective, randomised, multicentre trial was undertaken to determine whether greater rectal cancer downstaging and regression occurs when surgery is delayed to 12 compared to 6-weeks.

Methods: The primary endpoint was difference in proportion of patients in each arm downstaged according to MRI T-stage defined as any reduction in T-stage/sub-stage. A sample size of 218 patients was required. Secondary endpoints included pCR and mTRG 1-2 rates.

Results: A total of 237 patients were randomised: 122 (51%) into the 6-week and 115 (49%) to the 12-week arm. A significantly greater proportion downstaged in the 12-week arm (58%) compared with 43% in the 6-week arm (p = 0.019). The pCR rate was 9% in the 6-week versus 20% for the 12-week arm (p < 0.05). The mTRG 1-2 rate in the 6-week arm was 34% versus 52% in the 12-week arm (p < 0.05).

Conclusions: Waiting 12-weeks after CRT results in significantly more mTRG downstaging, pCR and improved mTRG. Since mTRG is a validated predictor of disease free survival, undertaking surgery before maximal regression may be disadvantageous.

Legal entity responsible for the study: N/A

Funding: Biomedical Research Centre

Disclosure: All authors have declared no conflicts of interest.

SCHEDULED USE OF CEA AND CT FOLLOW-UP TO DETECT RECURRENCE OF COLORECTAL CANCER: 6-12 YEAR RESULTS FROM THE FACSS RANDOMISED CONTROLLED TRIAL

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Background: The FACSS trial examined the use of CT imaging and carcinoembryonic antigen (CEA) measurements in the follow-up of patients with curatively treated colorectal cancer (R0 resection, stages I-III). The interim analysis showed that all intensive strategies (CEA, CT and CEA + CT) identified more recurrences treatable surgically with curative intent compared to minimum follow-up. There was no advantage in using both CT and CEA. This mature analysis reports overall survival (OS) results up to 12 years post randomisation comparing intensive (INT) to minimum (MIN) follow-up.

Methods: 1202 participants were randomised to 1 of 4 groups: regular CEA, regular CT imaging (chest abdomen pelvis), CEA + CT or minimum follow-up (symptomatic follow-up +/- single CT). Primary endpoint: surgical treatment of recurrence with curative intent. Follow-up concluded at 5 years, thereafter OS monitoring continued using registry data (median follow-up 8.7 years).

Results: Intensive follow-up identified more recurrences treatable with curative intent (INT 68/901 7.5% vs MIN 8/301 2.7%, p = 0.003). There was no difference in OS between groups (p = 0.45) but numerically more patients with recurrence were still alive in intensive groups (INT 43/901 4.8% vs MIN 7/301 2.3%, p = 0.07). Analysis of site of primary tumour revealed a similar proportion of curatively treatable recurrences in those with rectal tumours irrespective of follow-up (INT 27/275 9.8% vs MIN 6/67 6.9% p = 0.41). By contrast in those with a colon tumour treatable recurrence was more commonly detected by follow-up (INT 21/227 9.2% vs MIN 1/108 0.9% p = 0.1; right colon INT 14/282 5.0% vs MIN 0/104 0% p = 0.02). In participants with recurrence, OS benefit was only seen in those with a left colon tumour (median OS INT 4.4 years vs MIN 3.1 years p = 0.003).

Conclusions: Intensive follow-up increased the detection of treatable recurrence although further analysis suggested this was only the case for colon tumours. Furthermore, only patients with recurrence from a left colon tumour derived a survival advantage. This highlights the heterogeneous biology of colorectal cancer. It is unlikely that a survival benefit for the whole cohort will ever be shown.

Clinical trial identification: ISRCTN 41458548

Legal entity responsible for the study: University of Southampton

Funding: NIHR Health Technology Assessment Programme

Disclosure: All authors have declared no conflicts of interest.

A RANDOMIZED PHASE III STUDY OF NAPABUCIN [BBI608] VS PLACEBO (PBO) IN PATIENTS (PTS) WITH PREVIOUSLY TREATED ADVANCED COLORECTAL CANCER (ACRC): THE CCGT/AGITG CO.23 TRIAL

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Background: NAPA is a first-in-class cancer stemness inhibitor that targets STAT3, with promising activity in early trials.

Methods: Pts with ACRC who had failed all available standard therapy were randomized 1:1 to NAPA 480mg po q12h or PBO. Primary endpoint was overall survival (OS) Pre-specified biomarker analyses included pSTAT3 positivity by IHC in archival tissue based on nuclear staining of cancer cells ≥5% and stroma ≥2%. The study, designed to enrol 650 pts, was stopped after a futility analysis on disease control rate (DCR) in the first 96 pts. Analyses included Intent-to-treat (ITT) and exploratory Pre-defined Minimum Effective Treatment (pts who received ≥50% total daily dose for ≥6.4 weeks).

Results: 282 pts were randomized (138 NAPA, 144 PBO) from 04/2013 - 05/2014 when the trial was unblinded, accrual closed, and protocol treatment stopped after the futility analysis. Pts were median age = 64 (32 to 85); male = 65%; ECOG 0:1 (%): 28:72; >4 prior regimens = 98%; prior anti-VEGF = 89%; KRAS WT = 52%. No significant difference was observed in OS, progression free survival (PFS) or DCR between NAPA and PBO in the ITT analysis. At 48 weeks with NAPA included: any grade diarrhea (88 vs 32%), nausea (63 vs 47%), and anorexia (56 vs 46%), all p < 0.05; at least one AE ≥ grade 3 (57% vs 40%, p = 0.01) grade 3 (no grade 4) diarrrhea (17% vs 15%, p < 0.01). Diarrrhea was reversible upon NAPA hold. BORTEQL-QoL/C30 physical function at 8 wk deteriorated in 49% of pts on NAPA vs 29% on PBO (p = 0.038). Of 251 (89%) pts with pSTAT3 data, 55 (22%) were positive. In pts on PBO, pSTAT3 positivity was a poor prognostic factor (median OS 3.0 vs 4.9 mo, HR 2.3 (95% CI 1.5-3.6), p = 0.0002), but NAPA improved OS in pSTAT3 positive pts, HR 0.24.
abstracts

Table: 4S40

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<tr>
<th>Subset</th>
<th>Median OS (mos)</th>
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<td>1.13 [0.81-1.56], p = 0.34</td>
</tr>
<tr>
<td>NAPA</td>
<td>4.4</td>
<td>0.92 [0.64-1.31], p = 0.58</td>
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</table>

All Pts (n = 282)

pSTAT3 + (n = 55)  3.0  5.1  0.24 [0.12-0.51], p = 0.0002*

pSTAT3 - (n = 196)  4.9  4.0  1.44 [1.06-1.95], p = 0.02*  

All Pts (n = 128)  5.8  6.6  0.88 [0.61-1.28], p = 0.50

pSTAT3 + (n = 25)  4.0  9.0  0.28 [0.11-0.69], p = 0.0057*

pSTAT3 - (n = 88)  6.4  6.4  1.27 [0.80-2.01], p = 0.32*  

Results:
120 pts had prior chemotherapy for mCRC. 14 were enrolled in the first line. Most common adverse events were dermatitis acneeform, diarrhea, fatigue, nausea and rash. M. Ducreux respectively, were 10% and 8% for DP, 0% for TP and 18% and 67% for DTP. Median progression-free survival (PFS) for DP was 3.4 and 2.8 months, respectively. Median PFS for DTP is not yet mature. Median reduction in pERK in on-treatment vs pretreatment biopsies was 23% for DP, 50% for TP, and 54% for DTP. To date, no evidence of downstream target inhibition. CtDNA changes in on-treatment tumor biopsies were assessed for phosphorylated ERK (pERK) by IHC. Circulating tumor DNA (ctDNA) analysis of the BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E-mutated (BRAFm) metastatic colorectal cancer (mCRC)

Table 4S50

Efficacy and circulating tumor DNA (ctDNA) analysis of the BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E-mutated (BRAFm) metastatic colorectal cancer (mCRC)

Methods: 134 eligible pts with BRAFm mCRC received DP (n = 29), TP (n = 31), or DTP (n = 83) at up to full dose of each monotherapy agent. Pretreatment and on-treatment tumor biopsies were assessed for phosphorylated ERK (pERK) by IHC. Circulating DNA samples were profiled for mutations in BRAF, KRAS, NRAS, and PIK3CA.

Conclusions: In this trial, NAPA monotherapy did not improve OS or PFS in unselected ACR. While pSTAT3 positivity was a poor prognostic factor in untreated pts, NAPA treatment in pts with positive pSTAT3 significantly improved OS.

Legal entity responsible for the study: Canadian Cancer Trials Group (CCTG)

Funding: Canadian Cancer Society Research Institute (CCSRI) with funding support from Boston Biomedical Inc.

Disclosure: D. Jonker: Co-investigator on trials sponsored by Boston Biomedical Incorporated

BRAF V600E mutations occur in 5% to 10% of mCRC and confer poor prognosis. Unlike in BRAF V600–mutated melanoma, BRAF and MEK inhibitors have minimal activity in BRAFm mCRC. Preclinical studies suggest combined inhibition of the EGFR and MAPK pathway may improve efficacy in BRAFm mCRC. This study evaluates the safety and efficacy of P with D and/or T in BRAFm mCRC with integrated biomarker analyses.

Table 4S60

Circulating tumor DNA and circulating tumor cells as predictor of outcome in the PRODIGE14-ACCORD21-METHEP2 phase II trial

Methods: The trial enrolled colorectal cancer pts with potentially resectable liver metastases & no prior treatment; the primary endpoint was the rate of R0 liver metastases resection achieved by 1st line regimen (targeted therapies & bs- vs tri-chemotherapy; Ychou, ASCO 2016). Blood samples were collected at inclusion, after 1 month of therapy and before any liver metastases surgery. CTCs (CellSearch) & ctDNA (ddPCR, Biolead) were detected in an experienced laboratory (Inst. Curie).

Background: We prospectively detected circulating tumor DNA (ctDNA) and circulating tumor cells (CTC) levels in patients (pts) included in the PRODIGE14-ACCORD21-METHEP2 randomized phase II trial.

Conclusions:

Clinical trial identification: NCT01759018; first received by clinicaltrials.gov on December 6, 2012

Legal entity responsible for the study: Supported by GlaxoSmithKline. dabrafen and trametin are assets of Novartis AG as of 2 March 2015.

Funding: Supported by GlaxoSmithKline. dabrafen and trametin are assets of Novartis AG as of 2 March 2015.

Disclosure: R.B. Corcoran: Consultancy: Genentech, Merrimack, Ast, N-of-One, Andyth Nanomedicines, Tatio T. Andrus Consultancy Roche Honoro. Roche, Ams, Novartis. T. Yoshino: Research Funding: GlaxoSmithKline K.K., Boehringer Ingelheim GmbH. C.E. Atreya: Research Funding: GlaxoSmithKline, Novartis, Merck Membership on board of directors or advisory committees: Bayer Diagnostics, Genentech. M.P. Ducreux: Honoraria: Novartis, Roche, Merck, Ams, Lilly, Servier Speakers Bureau: Novartis, Roche, Merck, Ams, Lilly, Servier Membership on Board or Ad Committee: Novartis, Roche, Merck, Ams, Lilly, Servier Membership on Board or Ad Committee: Novartis, Roche, Servier Speakers Bureau: Novartis, Roche, Merck, Ams, Lilly, Servier


Conclusions: DTP had acceptable tolerability and activity in BRAFm mCRC, with evidence of downstream target inhibition. ctDNA changes in BRAF V600E mCRC may allow for monitoring of disease response and progression. Preexisting and emerging RAS mutations are potential mechanisms of resistance.

Clinical trial identification: NCT01759018; first received by clinicaltrials.gov on December 6, 2012

Legal entity responsible for the study: Supported by GlaxoSmithKline. dabrafen and trametin are assets of Novartis AG as of 2 March 2015.

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Disclosure: R.B. Corcoran: Consultancy: Genentech, Merrimack, Ast, N-of-One, Andyth Nanomedicines, Tatio T. Andrus, Consultancy Roche Honor. Roche, Ams, Novartis. T. Yoshino: Research Funding: GlaxoSmithKline K.K., Boehringer Ingelheim GmbH. C.E. Atreya: Research Funding: GlaxoSmithKline, Novartis, Merck Membership on board of directors or advisory committees: Bayer Diagnostics, Genentech. M.P. Ducreux: Honoraria: Novartis, Roche, Merck, Ams, Lilly, Servier Speakers Bureau: Novartis, Roche, Merck, Ams, Lilly, Servier Membership on Board or Ad Committee: Novartis, Roche, Merck, Ams, Lilly, Servier Membership on Board or Ad Committee: Novartis, Roche, Servier Speakers Bureau: Novartis, Roche, Merck, Ams, Lilly, Servier


Conclusions: DTP had acceptable tolerability and activity in BRAFm mCRC, with evidence of downstream target inhibition. ctDNA changes in BRAF V600E mCRC may allow for monitoring of disease response and progression. Preexisting and emerging RAS mutations are potential mechanisms of resistance.
**Results:** 153 pts had at least one blood analysis. High CTC count (≥23 CTC/5 ml) was detected in 25/152 pts (16%) at baseline and associated with synchronous liver metastases (p = 0.03) and of liver involvement (p = 0.001). At baseline, a 91% sensitivity of KRAS cDNA detection was observed (42/46 pts with KRAS mutated tumors, as determined per standard of care). In addition, 4 of 79 pts (5%) with tumors considered as KRASwt had >150 KRASmut copies/ml at baseline. After 1 month of therapy, only 3/108 pts (3%) had high CTC count and KRAS cDNA "sensitivity" dropped to 63/225 pts with KRAS mutated tumors. Among pts planned for liver metastases surgery, none had high CTC count before surgery (0/57) and cDNA "sensitivity" was 19% (4/21 pts with KRAS mutated tumors). Interestingly, persistently high CTC count (n = 0.06) and detectable KRAS mutated copies (p = 0.002) after 1 month of therapy were significantly associated with a lower R0/R1 liver metastasis resection rate (main study endpoint). Regarding overall survival, CTC count impacted OS at baseline and after 1 month of therapy (p = 0.001), while cDNA was a prognostic marker only before liver surgery (p = 0.0001).

**Conclusions:** This is the first study to assess CTC and cDNA clinical validity in pts with potentially resectable liver metastases. cDNA detection demonstrated excellent sensitivity and specificity, with a high positive predictive value. The major finding is that persistently elevated cDNA and CTCs after 1 month of therapy may help to select pts that won’t undergo later R0/R1 liver metastasis resection.

**Clinical trial identification:** NCT01442935

**Legal entity responsible for the study:** UNICANCER GI group

**Disclosures:** All authors have declared no conflicts of interest.

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**4570**

**MiR-31-3p is a predictive biomarker of cetuximab response in FIRE3 clinical trial**

P. Laurent-Puig,1 M.-L. Gislon,2 V. Heinemann,3 K. Fontaine,4 C. Vazart,1 V. Decaulne,2 F. Rousseau,2 B. Courtieu,2 F. Liebaert,2 A. Jung,4 D. Neureiter,5 R. Thiébaut2

**Background:** MiR-31-3p expression has been shown to be predictive of cetuximab efficacy on survival in RAS wild-type (WT) mCRC patients receiving anti-EGFR therapy in the FIRE-3 clinical trial. Patients were defined as low or high MiR-31-3p expressors based on a cutoff threshold defined in a previous study. When treated with cetuximab, patients with low miR-31-3p expression have a better survival than patients with high expression. We aimed to investigate the miR-31-3p predictivity on clinical endpoints on response.

**Methods:** MiR-31-3p expression was measured by qRTPCR after extraction from 370 RAS WT paraffin-embedded tumor samples. 191 patients were treated with FOLFIRI plus bevacizumab and 179 FOLFIRI plus cetuximab in first-line treatment. Objective response and disease control were analyzed in clinical centers based on RECIST criteria. An independent centralized radiological review reassessed patients for early tumor shrinkage (ETS) and Depth of response (DoR). ETS was defined as a diminution of 20% of the diameter at the first CT scan at 6 weeks after baseline. Response rates by treatment arms were compared through odds ratios estimated using logistic regression multivariate models. MiR-31-3p predictivity on response was assessed by testing interaction of treatment effect with miR-31-3p expression in low or high expressers groups (p = 0.10). When heterogeneity of treatment effect was detected, analyses were performed separately in both groups.

**Results:** A benefit of cetuximab therapy on objective response was seen only in low miR-31-3p expressors patients (OR = 3.37 [1.70-6.77], p = 0.0005 versus OR = 1.25 [0.56-2.77], p = 0.61 in high expressors). In low expressors, objective response rate was 70% in patients treated with cetuximab and 57% in patients treated with bevacizumab. Disease control rate was similar in the cetuximab arm and bevacizumab arms (80% and 86%, respectively), and homogeneous across miR-31-3p expression groups. MiR-31-3p expression is predictive of the DoS and ETS (interaction test: p = 0.0001 and p = 0.02 respectively).

**Conclusions:** Benefit of cetuximab on response is restricted to patients with low miR-31-3p expression. MiR-31-3p could be clinically useful to select patients for first line anti-EGFR therapy.

**Legal entity responsible for the study:** IntegraGen

**Funding:** IntegraGen


**ASBO**

**Funding:** EORTC charity trust

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**Table: 4580 Most frequent mutations according to location and MSI-H (%)**

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<th>Gene</th>
<th>MSS (n = 370)</th>
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<td>APC</td>
<td>77.8</td>
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| $ L vs R : p < 0.0001 |

**Conclusions:** Gene panel sequencing identified new potential therapeutic targets in an approximately total of 10% of patients with colorectal cancer. The SPECTA platform provides an effective platform for identifying rare, potentially actionable genomic targets.

**Clinical trial identification:** NCT01723969

**Legal entity responsible for the study:** EORTC

**Funding:** EORTC
POLE proofreading domain mutation defines a subset of immunogenic colorectal cancers with excellent prognosis

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Background: The delivery of precision cancer medicine depends on defining distinct tumour subgroups using biomarkers that may occur at very modest frequencies. One such subgroup comprises patients with exceptionally mutated (ultramutated) tumours caused by mutations that impair DNA polymerase epsilon (POLE) proofreading. While these mutants confer enhanced immunogenicity and excellent prognosis in the ~10% of endometrial cancers in which they occur, their consequences in colorectal cancer, where they are less common, are unclear.

Methods: We examined the association of POLE proofreading domain mutation with clinicopathological variables and immune response in colorectal cancers from the VICTOR, QUASAR2 and PETACC-3 clinical trials, and multiple patient cohorts (LUMC, Oslo, Bern, Switzerland, University College London, London, UK; Department of Medical Oncology, Centre Catalan d’Oncologia Clinique St. Pierre, Perpignan, France; Department of Gastroenterology and GI Oncology, European George Pompidou, Paris, France; Department of Oncology, University Hospital Center, Brussels, Belgium; Hepato-Gastroenterology Department, DJûnon University Hospital and INSERM U966, Fédération Françophone de Cancérologie Digestive (FFCD), Dijon, France; Department of Gastroenterology and Digestive Oncology, Hospital European George Pompidou, Paris, France).

Results: POLE mutations were detected in 66/6,448 (1.0%) colorectal cancers and were significantly associated with young age, male sex, right-sided location, early disease stage, and absence of mismatch repair deficiency (MMR-D) (P ≤ 0.003 for all associations). POLE-mutant tumours displayed increased CD8+ lymphocyte infiltration and expression of cytotoxic T cell markers and effector cytokines, similar to immunomodulatory MMR-D cancers. In multivariable analysis, POLE mutation was associated with a greatly reduced risk of cancer recurrence (HR = 0.34, 95%CI = 0.11 – 0.78, P = 0.006); particularly in stage II disease (HR = 0.22, 95%CI = 0.02 – 0.78, P = 0.04). This reduction appeared to exceed that associated with MMR-D (HR = 0.72 95%CI 0.60 – 0.87) – an established biomarker of favourable prognosis. Exploratory analysis suggested that the favourable outcome of POLE-mutant tumours was independent of chemotherapy.

Conclusion: POLE proofreading domain mutations identify a subset of immunogenic colorectal cancers with excellent prognosis. This novel biomarker holds promise to improve patient stratification in colorectal cancer.

Legal entity responsible for the study: Mark Gajewski

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Disclosure: M. de Bruyn: Funded by Dutch Cancer Society/Apel d’HuiZe grant RUG 2014-6719 S. Tejpar: Received research funding from Pfizer D. Kerr: Employee of, and owns stock in Oxford Cancer Biomarkers, has acted as a consultant for Amgen and Merck Serono, received speaker fees from Fresenius Kabi and research funding from Roche. All other authors have declared no conflicts of interest.
Background: RAS mutations have been shown to confer resistance to anti-EGFR treatment. We assessed here the results of the PETA3 trial (Cetuximab + FOLFOX vs FOLFOX in full wild type (WT) patients (pts) (RAS & BRAF)). The prognostic impact of mutations in rare RAS and BRAF mutations has been tested.

Methods: Exons 2, 3 and 4 of KRAS and NRAS as well as exons 11 and 15 of BRAF were tested. KRAS and NRAS are not encoded as exons 11 and 15. BRAF mutations were detected by sequencing exons 2, 3 and 4 of the KRAS gene as well as exons 11 and 15 of the BRAF gene. The extent of the mutational analyses is limited to the cancer cell types and some selected tissue samples, such as liver and the consequences of the mutations in the tissue and cell types are not systematic.

Results: Among the 3599 pts analysed, 745 (20%) were known to be mutated for KRAS exons 2 and 163 (4.6%) for BRAF V600E. From the remaining 1604 pts 104 had given informed consent for additional TR analyses and were NGS assessed, with 227 pts (21%) with mutated KRAS exons 2, 3 and 4 or NRAS exons 23, 4 and 4 (4.4%) as non-V600E BRAF mutated. Cetuximab was not improving significantly TTR, DFS or OS in pts with RAS WT or RAS & BRAF double WT mutants (HR: 0.63 [0.37-1.08]), and median DFS was 14.0 and 10.7 months (HR: 0.63 [0.37-1.08]), and median OS was 26.2 and 20.4 months (HR: 0.63 [0.37-1.08]). The impact of cetuximab is not significantly different with and without cetuximab in pts with RAS or BRAF rare mutations (HR ranging from 1.42 to 1.61, all p > 0.05). Pooling both treatment arms, as compared in double RAS & BRAF mutant pts (HR ranging from 1.13 to 1.29, all p > 0.05). Outcome was not significantly different with and without cetuximab in pts with RAS or BRAF rare mutations (HR ranging from 1.42 to 1.61). There were no differences in OS with RAS & BRAF double WT mutations (HR ranging from 1.13 to 1.17, all p > 0.05). The impact of cetuximab is not significantly different with and without cetuximab in pts with RAS or BRAF rare mutations (HR ranging from 1.42 to 1.61). There were no differences in OS with RAS & BRAF double WT mutations (HR ranging from 1.13 to 1.17, all p > 0.05).

Conclusions: In Stage III colon cancer, the addition of cetuximab to standard FOLFOX adjuvant therapy does not improve significantly outcome in RAS or RAS & BRAF wild type stage III colon cancer patients: Results from the PETA3 trial.
A multi-center, randomized, double-blind phase II trial of FOLFIRI + regorafenib or placebo for patients with metastatic colorectal cancer who failed one prior line of oxaliplatin-containing therapy


Method: The COBRA-III study was an open-label, randomized, double-blind, phase II trial to compare the efficacy and safety of regorafenib vs placebo in patients with mCRC who were refractory to oxaliplatin-containing chemotherapy. The trial included 194 patients who had failed two or more lines of treatment for mCRC. The primary endpoint was progression-free survival (PFS). The study was conducted at 45 centers in the United States and Ireland.

Results: The median PFS was 5.9 months in the regorafenib group versus 2.3 months in the placebo group (HR 0.67; 95% CI 0.51-0.88; P = 0.003). The difference was statistically significant (P = 0.002). The overall response rate (ORR) was 12% in the regorafenib group versus 5% in the placebo group (P = 0.038). The disease control rate (DCR) was 79% in the regorafenib group versus 55% in the placebo group (P = 0.001). The median overall survival (OS) was not reached in the regorafenib group versus 17.3 months in the placebo group (HR 0.70; 95% CI 0.50-0.99; P = 0.044). The safety profile was consistent with the known safety profile of regorafenib, with grade 3/4 adverse events including diarrhea (34%), hand-foot syndrome (20%), and proteinuria (5%).

Conclusion: Regorafenib was effective and well-tolerated in patients with mCRC who failed two or more lines of chemotherapy. The PFS and OS were significantly improved with regorafenib compared to placebo. These results support the use of regorafenib in this patient population.
Background: Sorafenib and irinotecan combination (NEXIRI) showed promising efficacy with a 65% disease control rate (DCR) in pretreated mutated (mt) KRAS mCRC patients: a multicentre randomized phase II trial (NEXIRI 2-PRODIGE 27). The combination of NEXIRI was proposed as a candidate predictive biomarker for this combination.

Methods: Patients PS ≤ 1 with progressive or non-reactor mtKRAS (then RAS) mCRC pretreated with irinotecan, oxaliplatin, fluoroquinolones, and bevacizumab (none with regorafenib), were randomized in 3 arms: NEXIRI (irinotecan 180mg/m², sorafenib 400 mg BID) vs Iri (180 mg/m²) alone or Soraf (400 mg BID) alone. The primary endpoint was the 2-month progression-free survival (2-PFS).

Results: We included 173 patients (age 62 years; 31-82; PS 0-1: 38/61%) between January 2012 and July 2014 in 17 French centres. Main results were (median follow-up 17.5 months): Overall survival (OS) 17.5 months) and progression-free survival (PFS) 5.9 months; 2-PFS (%$ 59 [39-66] versus 23 [10-33] versus 22 [8-30] versus 51 [30-54]; DCR/PR (%)$ 59/4 versus 25/0 versus 22/0 versus 51/1.

Conclusions: The TERRA study demonstrated an improvement in OS and PFS in Asian pts with mCRC who had failed conventional cytotoxic therapies. The safety profile of TAS-102 was similar to that in previous studies. A data according to the pre and post-study treatments, especially targeted therapies, will be presented.

Clinical trial identification: NCT01955837

Legal entity responsible for the study: Taiho Pharmaceutical Co., Ltd.

Funding: Taiho Pharmaceutical Co., Ltd.


Funding: Grant from the Bayer laboratories.

Disclosure: E. Samalin: Honoraria: Lilly, Sanofi, Amgen, Roche Consulting or Advisory Role: Amgen, Sanofi, Roche Research funding: Bayer (Institution) Travel, Accommodations, Expenses: Novartis, Lilly, Ipsen, Roche C. de la Fouchardiere: Consulting or Advisory Role: Amgen, Lilly, Bayer, Roche Research Funding: Roche Travel, Accommodations, Expenses: Roche, Colgene, Amgen, V. Boige: Honoraria: Bayer, Sorafenib, Merk-Serono, Daichi Sankyo Consulting or Advisory Role: Bayer, Amgen Research Funding: Merk-Serono Travel, Accommodations, Expenses: Merck Serono, Amgen, H. Serenari: Consulting or Advisory Role: Boehringer Ingelheim, Merck, Roche Travel, Accommodations, Expenses: Roche, Pfizer: R. Guimbard: Consulting or Advisory Role: Ipsen Research Funding: Roche/Genentech (institution) J. Taieb: Honoraria: Merck, Amgen, Lilly, Sanofi, Colgene, Roche Travel, Accommodations, Expenses: Merck, Amgen, Roche, M.P. Galais: Honoraria: Roche, A. Adenis: Consulting or Advisory Role: Bayer, Sanofi Speaker’s Bureau: Roche/Genentech Research Funding: Bayer (Institution), Sanofi (Institution). A. Lлеве: Honoraria: Merck-Serono, Sanofi, Lilly, Amgen, Roche Consulting or Advisory Role: Merck-Serono, Sanofi, Lilly, Roche Speaker’s Bureau: Colgene Travel, Accommodations, Expenses: Merck-Serono, Amgen, Lilly, Roche: F. Di Fiono: Honoraria: Merck, Amgen, Sanofi, Bayer, Novartis, Lilly, Colgene, Roche Research Funding: Amgen (Institution), Merck (Institution), Roche (Institution). F. Bibeu: Honoraria: Amgen, Merck, Sanofi, Roche Consulting or Advisory Role: Amgen, Sanofi Research Funding: Roche (Institutions) Travel, Accommodations, Expenses: Amgen, Merck, Roche T. Mazard: Honoraria: Amgen, Sanofi Research Funding: Roche Parma AG (Institution) Travel, Accommodations, Expenses: Amgen, M. Ychou: Honoraria: Bayer, Merck, Roche Consulting or Advisory Role: Bayer, Merck, Roche All other authors have declared no conflicts of interest.

TAS-102 group (44.1% versus 14.6%). Most frequent Grade ≥ 3 treatment-emergent adverse events (TEAEs) were neutropenia (20.3% in TAS-102, 0% in placebo), anemia (15.9%, 9.5%) and leukopenia (4.8%, 0%).

Conclusions: The TERRA study demonstrated an improvement in OS and PFS in Asian pts with mCRC who had failed conventional cytotoxic therapies. The safety profile of TAS-102 was similar to that in previous studies. A data according to the pre and post-study treatments, especially targeted therapies, will be presented.

Clinical trial identification: NCT01955837

Legal entity responsible for the study: Taiho Pharmaceutical Co., Ltd.

Funding: Taiho Pharmaceutical Co., Ltd.

Disclosure: T.W. Kim: Employment, leadership, Tock, Speaker’s bureau, patients, expert testimony Travel expenses: No Research fund: Roche, Merck Serono Consulting or advisory role: Bayer, Lilly All other authors have declared no conflicts of interest.

Table: 468PD

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<td>Grade 3/4 toxicities (%)</td>
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<td>2-PFS (%)a</td>
<td>59 (39-66)</td>
<td>23 (10-33)</td>
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<td>DCR/PR (%)a</td>
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<td>51/1</td>
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<td>Median PFS (months)</td>
<td>3.7 (2.2-4.9)</td>
<td>1.9 (1.7-2.1)</td>
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<td>Median OS (months)</td>
<td>7.2 (5.8-9.4)</td>
<td>3.0 (2.1-3.8)</td>
<td>3.3 (2.5-4.2)</td>
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<td>A/A vs mCRC</td>
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<td>1.4 (1-4)</td>
<td>3.0 (2.4-3)</td>
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<td>3.3 (2-4.2)</td>
<td>7.5 (5.6-8.5)</td>
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*170 patients; †18 (6/4/8/12) non-evaluable patients; ‡montotherapies alone, patients who did not cross. Pharmacokinetics results showed an increase of the irinotecan plasma concentration with the addition of Sorafenib for patients in the Nexi and cross-over arms.
abstracts

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Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin vs. capecitabine alone in locally advanced rectal cancer: final analyses


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Background: The PETACC-6 trial investigates whether the addition of oxaliplatin to preoperative oral fluoropyrimidine-based chemoradiation (CRT) followed by postoperative fluoropyrimidine-based chemotherapy (CT) improves disease-free survival (DFS) in locally advanced rectal cancer.

Methods: Between 11/2008 and 09/2011, patients with rectal adenocarcinoma within 12 cm from the anal verge, with no evidence of metastatic disease and considered either resectable at the time of entry or expected to become resectable, were randomly assigned to receive 5 weeks of preoperative CRT with capecitabine, followed by 6 cycles of adjuvant CT with capecitabine with (arm 2) or without (arm 1) the addition of oxaliplatin before and after surgery. 440 DFS events were required to have 80% power to detect an improvement in 3-year DFS from 65% with capecitabine alone to 72% with capecitabine and oxaliplatin (HR = 0.763) using a two-sample log-rank test with a significance level of 0.05 and 80% power for each arm.

The primary analysis was intent-to-treat, adjusted for stratification factors (clinical T stage, nodal status, distance from the tumor to the anal verge and method of locoregional staging) except center.

Results: 1094 patients randomized (547 each arm), 543 eligible patients (arm 1), 526 (arm 2) started treatment; 67.4% completed protocol treatment in arm 1 vs. 53.8% in arm 2; 10% patients had a major protocol deviation.

Conclusions: A retrospective, central evaluation of FIRE-3...
Disclosure: Funding: less than 0.025. Thus, with regard to the optimal duration of adjuvant chemotherapy, p-values of OS and RFS comparing 48 weeks treatment with 24 weeks treatment were not demonstrated in patients with stage III colon cancer. However, the JFMC37-0801 study was planned to offer superiority of 48 weeks of adjuvant chemotherapy compared to 24 weeks of treatment. The primary endpoint was disease-free survival in patients with stage III colon and rectosigmoid cancer. Here, we report the final results of this study.

Methods: Patients with curatively resected stage III colon and rectosigmoid cancer (PS, 0 to 1; age, 20 to 79 years; no other therapy) were randomly assigned to receive capecitabine (1,250 mg/m^2/day) for 14 out of 21 days for 24 weeks, 8 courses (Control arm) or for 48 weeks, 16 courses (Study arm). The primary endpoint was DFS and the secondary endpoints were overall survival (OS) and relapse free survival (RFS).

Results: At the time of this final analysis, median follow-up was 60 months with 434 DFS events out of 1,504 (C: 654, S: 650) pts. The 3-year and 5-year DFS for the primary endpoint was 75.3%, 68.7% in the S arm and 70.0%, 65.3% in the C arm, respectively (p = 0.0068, HR = 0.866, 95%CI: 0.717-1.064). The 5-year OS was 87.6% in the S arm and 83.2% in the C arm (p = 0.0195, HR = 0.737, 95%CI: 0.535-0.975). The 5-year RFS was 74.1% in the S arm and 69.3% in the C arm (p = 0.0207, HR = 0.808, 95%CI: 0.658-0.992). Overall grade 3-4 adverse events of S arm were comparable with those of C arm except increasing hand-foot syndrome.

Conclusions: DFS superiority in 48 weeks treatment of capecitabine adjuvant chemotherapy was not demonstrated in patients with stage III colon cancer. However, p-values of OS and RFS comparing 48 weeks treatment with 24 weeks treatment were less than 0.025. Thus, with regard to the optimal duration of adjuvant chemotherapy for stage III colon cancer, further investigation was considered to be needed.

Legal entity responsible for the study: N/A

Funding: Japanese Foundation for Multidisciplinary Treatment of Cancer

Disclosure: All authors have declared no conflicts of interest.

Efficacy and safety of cobimetinib (atezo) and atezolizumab (atezo) in an expanded phase 1b study of microsatellite-stable (MSS) metastatic colorectal cancer (mCRC)

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Background: MSS colorectal cancers, which comprise the vast majority of mCRC patients (ps), appear essentially resistant to PD-L1/PD-1 blockade in many other tumors. Since inhibitors of MEK promotes T cell accumulation intratumorally and combines with anti-PDL1 pre-clinically (Ebert, Immunity 2016), the combination of cobimetinib (MEK inhibitor) and atezolizumab (anti-PDL1) was evaluated in its mCRC.

Methods: 44 mCRC pts were enrolled with 23 evaluable pts for efficacy, including 22 KRAsmt and 1 KRAvpt, who failed prior lines of therapy and were not selected by PD-L1 expression. Of these 23 pts, 3 were treated with cobi during escalation. (at 2 and mg. 1 at 60 mg) and 20 were treated during expansion (60 mg). Cobi was dosed PO for 21 of 07/17 off and atezo at 800 mg IV qw2. Primary endpoints were safety and tolerability. Secondary endpoints included investigator-assessed efficacy by RECIST v1.1. MSS status was confirmed by mutation load profiling.

Results: As of Feb 12, 2016, the 23 efficacy evaluable mCRC pts had a median safety follow-up of 3.78 mo (range, 1.1-15.1). None were identified as MSI-H and the majority expressed low levels of PD-L1 at baseline. The 6 mo survival rate was 72% (95% CI: 52, 93). Confirmed responses were seen in 4 pts (17%) with duration ranging from 5.4 to 11.1 mo and were ongoing in 2 pts. Activity did not correlate with PD-L1 expression. All grade treatment-related AEs occurring in > 20% pts included diarrhoea, fatigue, dermatitis acnestiform, rash, maculopapular rash, pruritus, nausea, creatine phosphokinase increase and AST elevation consistent with that seen for the single agents. G3-4 AEs related to either drug were seen in 8 pts (34.8%). The most common individual, related G3-4 AEs (diarrhoea and rash) occurred in ≤ 2 pts (8.7%). No G5 AEs occurred. Four AEs led to discontinuation of cobi. No AEs led to atezo withdrawal. Updated biomarker data including anti-tumor immune markers will be presented.

Conclusions: In chemotherapy-refractory MSS mCRC where single-agent cobi and atezo have shown minimal activity, encouraging early results with the combination are observed for ORR, DOR, and 6 mo survival. Further trial follow-up is ongoing.

Clinical trial identification: NCT01988896

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: J.R. Infante: I have no personal financial conflicts of interest but my institution receives research funding and consulting from Genentech. J. Wallin, M. Das Thakur, G. Mwawasi, P. Foster, E. Chu: Genentech employee. All other authors have declared no conflicts of interest.
A multicentre phase I/II study of TAS-102 with nintedanib in patients with metastatic colorectal cancer refractory to standard therapies (N-TASK FORCE: EPOC1410): Phase I results

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Background: TAS-102 is an oral nucleoside antitumor agent, which demonstrated significant improvement in overall survival over placebo in patients (pts) with metastatic colorectal cancer (mCRC). Nintedanib is a triple angiokinase inhibitor of VEGFR (1, 2, 3), PDGFR (α, β), and FGFR (1, 2, 3). A global phase III study is ongoing to compare nintedanib with placebo in pts with mCRC resistant to standard therapies. In preclinical models, the combination of TAS-102 plus nintedanib demonstrated enhanced activity against CRC compared with either drug alone (Suzuki N, et al. AACR 2016). This study investigates efficacy and safety of TAS-102 with nintedanib and herein we present the results of the phase I part.

Methods: The key eligibility criteria were pts with mCRC refractory or intolerant to fluorouracil, irinotecan, oxaplatin, anti-angiogenesis inhibitor and anti-EGFR antibody (flid type-RAS) and without prior regorafenib. Phase I part was designed to determine the recommended phase II dose (RP2D) in a 3 × 3 cohort-based dose escalation design of nintedanib (150mg BID every on level 1 and 200mg BID every on level 2) in combination with standard dose of TAS-102.

Results: Three patients were treated in level 1, and 6 pts in level 2. No dose-limiting toxicities were observed at either level. The most common grade 3 or worse treatment-associated adverse events were neutropenia (67%), anemia (33%), and increased liver enzymes (22% asymptomatic reversible grade 3 AST/ALT elevation without any bilirubin elevation). The disease control rate was 100%, and 8 pts (89%) showed any tumor shrinkage including one partial response (Suzuki N, et al. AACR 2016). The relative dose intensity was 86.4% for TAS-102 and 89.8% for nintedanib. Drug-drug interaction was not indicated by pharmacokinetic analysis.

Conclusions: Standard dose of TAS-102 with nintedanib 200 mg BID was tolerable and determined as RP2D. This combination regimen had a promising antitumor activity, which will be confirmed by ongoing phase II part.

Clinical trial identification: Clinical trial information: UMIN000017114. Release date: 13/April/2015

Legal entity responsible for the study: Declaration of Helsinki, Ministerial Ordinance on Good Clinical Practice

Funding: Boehringer Ingelheim


Targeting FGF2 expression against chemoresistance in colorectal cancer (CRC) cell lines - a potential prognostic biomarker in patients with metastatic colorectal cancer (mCRC) treated with FUFIRI or mIROr (FIRE1)

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Background: Our aim was to evaluate fibroblast growth factor 2 (FGF2) expression in cultured CRC cell lines exposed to 5-fluorouracil (5-FU) and validate results with clinical data from mCRC patients receiving first-line chemotherapy.

Methods: 5-FU IC50 was determined in CRC cell lines DLD1, LoVo, and HCT-15 applying MTT assays. mRNA expression of FGF2 was measured by RT-qPCR with HPRT as reference gene. Threshold values were determined by minimum p-value method. FGF2 expression was knocked down by sh (short hairpin) RNA in vitro. FGFR receptor (FGF-R) was inhibited using Dovitinib with DMSO as control. In vitro results were then translated on the randomized FIRE1 trial (5-FU/LV/irinotecan [FUFIRI] vs. irinotecan/oxaliplatin [mIROr] using Nanosmart technology. 187 patients were included in this analysis.

Results: 48 h incubation of CRC cell lines with 5-FU showed an increase of FGF2 expression [DLD1: 1.98-fold, p < 0.001; LoVo: 3.51-fold, p < 0.001; HCT-15: 1.96-fold, p < 0.002]. Knockdowning FGF2 expression [loss of FGF2 expression: DLD1: 86%, p = 0.008; LoVo: 97%, p = 0.03; HCT-15: 82%, p = 0.04] correlated with a significant decrease of IC50 for 5-FU in CRC cell lines [DLD1: 23.52 to 15.27 µM, p < 0.023; LoVo: 28.96 to 15.23 µM, p < 0.001; HCT-15: 34.40 to 21.12 µM, p = 0.005]. 72 h incubation with Dovitinib led to a total growth restriction in all CRC cell lines compared to control (DMSO). In FIRE1, high (n = 89) vs. low (n = 98) FGF2 expression was not correlated significantly with PFS [8.0 vs. 8.2 months, HR: 0.87, 95% CI 0.65 – 1.17, p = 0.37] but with OS [17.9 vs. 23.5 months, HR: 0.70, 95% CI 0.51 – 0.96, p = 0.025] in FUFIRI and mIROr. Higher FGF2 expression was significantly associated with objective response rate [PR and CR (n = 84) vs. SD and PD (n = 21); 24.85 vs. 31.89, p = 0.049].

Conclusions: FGF2 expression might reflect chemoresistance in CRC cell lines as a knockdown of FGF2 led to a decrease of IC50 for 5-FU in vitro. In FIRE1, high FGF2 expression was associated with lower response rate and overall survival significantly. Interfering the FGF2 system might be a modulator for acquired chemoresistance.

Legal entity responsible for the study: Department of Medicine III, University of Munich, Institute of Pathology, University of Munich

Funding: Weigand-Bohnenwald-Gravenhorst-Fond, University of Munich

Disclosure: All authors have declared no conflicts of interest.

A phase I study to determine the effect of regorafenib (REg) on the pharmacokinetics (PK) of substrates of P-glycoprotein (P-gp; digoxin) and breast cancer resistant protein (BCRP; rosuvastatin) in patients with advanced solid tumors

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Background: REG is an oral multikinase inhibitor approved for the treatment of mCRC and advanced GST. In vitro data showed that REG has an inhibitory effect on BCRP and P gp transporters. A study was designed to evaluate the effect of REG on the PK of digoxin (P-gp substrate) and rosuvastatin (BCRP substrate).

Methods: This was an open-label, non-randomized, 2 parallel group study to compare the PK of the P-gp substrate digoxin (group A) and BCRP substrate rosuvastatin (group B) with and without REG. Oral REG 160 mg QD was administered in 28-day cycles (3 weeks on/1 week off). On pre-cycle Day -7 and cycle 1 Day 15, patients received a single oral dose of digoxin (0.5 mg, group A) or rosuvastatin (5 mg, group B), and serial plasma samples were collected for PK analysis.

Results: 42 patients were treated and 30 patients were evaluable for PK analysis (17 in group A, 13 in group B). There was no relevant change in mean AUC0–24h and Cmax of digoxin (<15% change) when co-administered with REG, as reflected in a least square (LS) mean ratio of 1.05 for AUC0–24h and 1.12 for Cmax. Co-administration of REG with rosuvastatin significantly affected the exposure of rosuvastatin (LS mean ratio of 3.32 for AUC0–24h and 4.55 for Cmax). The most common REG-related adverse events were hand-foot skin reaction (40%), fatigue (36%), hypertension (33%), diarrhea (29%), hyperbilirubinemia (24%), and decreased appetite (24%). Three patients (2 adenocarcinoma of the cardia, 1 colon carcinoma) had partial response and 10 had stable disease.
Phase II clinical trial with axitinib as maintenance therapy in patients (p) with metastatic colorectal carcinoma (CRC)

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Background: The prognosis of advanced CRC has improved during last years. Nevertheless, treatment options in this situation are still limited. Maintenance therapy with bevacizumab has been standard of care after bevacizumab plus fluoropyrimidine based chemotherapy. Axitinib is a novel drug targeting VEGFR1, 2 and 3, with contradictory results in CRC.

Methods: In this phase 2 randomized double blinded trial, axitinib (5 mg/bid) was compared to placebo in metastatic CRC p who had not progressed after 6 months of first line treatment with chemotherapy with or without bevacizumab or cetuximab. The primary objective was progression-free survival (PFS) at 6 months. Secondary objectives included overall survival (OS), response rate (RR) and safety.

Results: A total of 49 p were included: 25 cohort A (axitinib) and 24 cohort B (placebo). Baseline characteristics were well balanced. Mean age was 66 years (Standard Deviation (SD) ±10.39), 33 (67%) were men; ECOG Performance status was 0 for 33 p (67%), 1 for 10 p (20%) and 2 for 6 p (12%). The most frequent treatment exposure to BCRP substrates. The safety profile was consistent with the known safety profile of axitinib.

Clinical trial identification: NCT02106845

Legal entity responsible for the study: Iber.

Funding: Bayer


Phase II trial to Study Bevacizumab and Cetuximab in Combination with Chemotherapy After Progression to FOLFIRI in Patients with Metastatic Colorectal Cancer After Bevacizumab and/or Cetuximab Therapies


Background: We have previously conducted a phase I study of preoperative concurrent chemoradiotherapy combining S-1 and irinotecan with radiotherapy of the lesser pelvis in patients with resectable, locally advanced rectal cancer (SAMRAI-1 Trial). The maximum tolerated dose (MTD) of axitinib was 80 mg/m2, and the recommended dose was 60 mg/m2. We thus conducted a phase II study (SAMRAI-2 Trial) to further evaluate efficacy and safety.

Methods: We studied patients 20–80 years of age with a performance status of 0 or 1 who had clinical stage T3 or 14, N0–3, M0, N2, 12, resectable cancer (adenocarcinoma) of the upper rectum (Ra) or lower rectum (Rb). The treatment schedule was irinotecan 60 mg/m2 on days 1, 8, 22, and 29; S-1 80 mg/day (body surface area, <1.25 m2), 100 mg/ day (1.25 m2 ≤ S ≤ 1.5 m2) on days 1–5, 8–12, 22–26, and 29–33, and radiotherapy 1.8 Gy/day on days 1–5, 8–12, 19–22, and 29–33 (total, 45 Gy). The primary endpoint was the pathological complete response (pCR) rate. Assuming a threshold pCR rate of 10% with an expected value of 25%, a power of 90%, and a one-sided alpha level of 10%, we set the target number of patients at 40.

Results: From October 2013 through February 2015, 43 patients were enrolled, and 41 were eligible and treated. The mean age was 57.9 years (range, 41 to 72). The male:female ratio was 30:11. The disease stage was IB in 15 patients, IIIB in 15, IIIC in 2, and IIIC in 2. The tumor site was Rb in 24 patients, Rab in 7, Rba in 4, and RbP in 12. The median dose administered was 80 mg/m2. We thus conducted a phase II study (SAMRAI-2 Trial) to further evaluate efficacy and safety.

Legal entity responsible for the study: Iber.

Funding: None


A multicenter phase II study of preoperative concurrent chemoradiation therapy with S-1 plus irinotecan for locally advanced rectal cancer: SAMRAI-2


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Background: We previously conducted a phase I study of preoperative concurrent chemoradiation therapy combining S-1 and irinotecan with radiotherapy of the lesser pelvis in patients with resectable, locally advanced rectal cancer (SAMRAI-1 Trial). The maximum tolerated dose (MTD) of axitinib was 80 mg/m2, and the recommended dose was 60 mg/m2. We thus conducted a phase II study (SAMRAI-2 Trial) to further evaluate efficacy and safety.

Methods: We studied patients 20–80 years of age with a performance status of 0 or 1 who had clinical stage T3 or 14, N0–3, M0, N2, 12, resectable cancer (adenocarcinoma) of the upper rectum (Ra) or lower rectum (Rb). The treatment schedule was irinotecan 60 mg/m2 on days 1, 8, 22, and 29; S-1 80 mg/day (body surface area, <1.25 m2), 100 mg/ day (1.25 m2 ≤ S ≤ 1.5 m2) on days 1–5, 8–12, 22–26, and 29–33, and radiotherapy 1.8 Gy/day on days 1–5, 8–12, 19–22, and 29–33 (total, 45 Gy). The primary endpoint was the pathological complete response (pCR) rate. Assuming a threshold pCR rate of 10% with an expected value of 25%, a power of 90%, and a one-sided alpha level of 10%, we set the target number of patients at 40.

Results: From October 2013 through February 2015, 43 patients were enrolled, and 41 were eligible and treated. The mean age was 57.9 years (range, 41 to 72). The male:female ratio was 30:11. The disease stage was IB in 15 patients, IIIB in 15, IIIC in 2, and IIIC in 2. The tumor site was Rb in 24 patients, Rab in 7, Rba in 4, and RbP in 12. The median dose administered was 80 mg/m2. We thus conducted a phase II study (SAMRAI-2 Trial) to further evaluate efficacy and safety.

Legal entity responsible for the study: Iber.

Funding: None


None

Funding: None
KRAS wildtype (KRASwt) metastatic colorectal cancer (mCRC). Pre-clinical studies have demonstrated activity of temozolomide (TMZ) in mCRC cell lines (Inoue et al, World J Clin Cases 2014), and clinical phase 2 data indicate efficacy of TMZ in heavily pre-treated mCRC patients (Scacham-Shmueli et al, ECO 2011, Pietrantoni et al, Ann of Oncol 2014, Pietrantoni et al, Targ Oncol, 2015). The combination of TMZ and capcitabine (TMZ-Cap) have synergistic schedule-depende effect (Fine et al, ASCO 2005). Therefore we initiated and completed two parallel phase II studies on the combination of TMZ-Cap in heavily pre-treated mCRC patients with KRASwt and KRASmut mCRC, respectively. Data on the combination of TMZ-Cap in KRASmut patients was recently presented (Qvortrup et al, ESMO 2015).

**Methods:** Phase II study evaluating the combination of capcitabine (2000 mg/m² days 1-14) with TMZ (150 mg/m² days 10-14) every 4 weeks in patients with refractory mCRC.

**Results:** Forty patients with refractory KRASwt mCRC from 3 Danish oncological departments were included from June 2013 to October 2015. Median age was 65 years (47-77), 33% were women. No patients achieved PR, ORR was 1.9 (1.7-3.4) months, and mOS was 7 (5.8-9.7) mo. Toxicity was modest, only 1 patient stopped therapy due to toxicity.

**Conclusions:** The combination of TMZ and capcitabine is safe and has activity comparable to regorafenib and TAS-102 in patients with heavily pre-treated KRASwt mCRC. A search for predictive markers including MGMT expression is ongoing.

**Clinical trial identification:** EUDRACT: 2012-003273-15

**Legal entity responsible for the study:** Clinical Research Unit at department of Oncology Odense University Hospital

**Funding:** Clinical Research Unit at department of Oncology Odense University Hospital

**Disclosure:** All authors have declared no conflicts of interest.

**Legal entity responsible for the study:** Sponsored by Bristol-Myers Squibb

**Funding:** Sponsored by Bristol-Myers Squibb

**Disclosure:** H. J. Lenz: Has served as a consultant/advisory board member and received travel expenses from Bayer, Merck Serono, and Roche. He has received honoraria from Bayer, Boehringer Ingelheim, Celgene, Merck Serono, and Roche. P. Garcia-Alfonso: Has served on advisory boards for Boehringer, Merck, Sanofi, Amgen, Bayer, and Lilly. A. Hill: is employed by, owns stock in, and has received research funding from Tasman Oncology Research. He has received travel accommodations/expenses from BMS. R. A. Moss: Is employed by and owns stock in Bristol-Myers Squibb. M. V. Goldberg, C-S. Lin, H. Tang: Is an employee of Bristol-Myers Squibb. T. André: Has received honoraria from BMS and consultant fees from Roche. All other authors have declared no conflicts of interest.

**Background:** Globally, about 10% of new cancers each year are CRC and ~15% of these are MSI-H. Nivolumab (N), a fully human anti-PD-1 mAb, and ipilimumab (I), a humanized anti-CTLA-4 mAb, are immune checkpoint inhibitors with favorable safety and efficacy profiles in multiple tumor types. This phase 2 study evaluates N ± I in MSI-H and non-MSI-H pts with mCRC.

**Methods:** MSI-H pts received N 3.5 mg/kg q2 wk (N3) or N 3 mg/m² q1 mg/kg q3 wk (N3 + I1) x 4 doses followed by N3 until disease progression (PD) or other discontinuation. Initial evaluation of N + I was also completed in non-MSI-H pts. Primary endpoint was investigator-reported ORR by RECIST 1.1. Other endpoints included safety, OS, PFS, and clinical activity in biomarker-defined subpopulations (KRAS, BRAF, status, and PD-L1).

**Results:** 35 (N3) and 30 (N3 + I1) MSI-H pts and 13 (N1 + I1), 10 (N1 + I), and 10 (N3 + I1) non-MSI-H pts were enrolled. All non-MSI-H pts and 87% (N3) and 93% (N3 + I1) of MSI-H pts had ≥2 prior regimens. 47% (N3) and 18% (N3 + I1) MSI-H pts remain on tx. Efficacy data for MSI-H pts are shown in the Table. Responses were also seen in non-MSI-H pts. Median (95% CI) PFS across all non-MSI-H pts was 1.4 mo (1.2, 1.9). Responses were observed regardless of tumor PD-L1 expression. Treatment-related adverse events (TRAEs) occurred in 41 (59%; N3) and 25 (83%; N3 + I1) MSI-H pts and 10 (14%; N3) and 8 (27%; N3 + I1) pts had Grade 3-4 TRAEs. One pt on N3 had a Grade 3 TRAE (sudden death). Additional biomarker data including MSI assessment and influence of BRAF/KRAS mutations will be presented.

**Conclusions:** N ± I demonstrated promising clinical activity with a favorable overall safety profile in pts with mCRC regardless of tumor PD-L1 expression. Additional biomarker analyses are ongoing.

<table>
<thead>
<tr>
<th>N3 (n = 70)</th>
<th>N3 + I1 (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>12 (25.5)</td>
</tr>
<tr>
<td>CR PR, n (%)</td>
<td>0/2 (25.0)</td>
</tr>
<tr>
<td>Median DOR (95% CI), mo</td>
<td>14 (28.9) 17 (36.2) 4 (8.5)</td>
</tr>
<tr>
<td>NE, NE</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>NE, NE</td>
<td>9 (33.3) 14 (41.9) 3 (11.1) 1 (3.7)</td>
</tr>
<tr>
<td>NE, NE</td>
<td>66 (45.5, 81.1) NR</td>
</tr>
<tr>
<td>NE, NE</td>
<td>85 (65.0, 94.2) 85 (65.0, 94.2) 85 (65.0, 94.2) 85 (65.0, 94.2)</td>
</tr>
<tr>
<td>NE, NE</td>
<td>7 (23.0) 20.6 (67.7) 10 (0.0)</td>
</tr>
</tbody>
</table>

**Table: 479P. MSI-H**

**Efficacy**

By local screen

*Reported for patients with 12 weeks of follow-up, N3 (n = 47) and N3 + I1 (n = 27)
The correlation between tumor regression grade and retrieved lymph nodes status in locally advanced rectal cancer after neoadjuvant treatment: results from a prospective study

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Disclosure: No conflicts of interest.

Background: A paucity of lymph nodes harvested is common in rectal cancer after neoadjuvant treatment and the significance is still uncertain. We aimed to evaluate the correlation between tumor regression grade (TRG) and retrieved MEK/METi expression in a 28 day cycle. The combination is now being explored further with an alternate MEK5 before expansion into RASMT and RASW TRC with aberrant C-MET expression. EudraCT registry number: 2014-000463-40

Methods: A prospective phase I trial of PD-0325901 with crizotinib in patients with advanced solid tumours using NCI CTCAE V4.03. Data were collected from 1 July 2014 to 30 November 2015. Addition of epidermal growth factor receptor inhibitors to chemotherapy improves objective response rates (ORR) and may improve resection rates but their role in pts requiring disease control is less clear. This exploratory analysis from the PRIME trial assessed the efficacy of panitumumab (pmab) with FOLFOX4 according to the goal of treatment (cytoreduction or disease control). MTD was defined at the highest dose; crizotinib: 8mg BD (days 1-21) and 200mg BD continuously in a 28 day cycle. The combination is now being explored further with an alternate MEK5 before expansion into RASMT and RASW TRC with aberrant C-MET expression. EudraCT registry number: 2014-000463-40

Results: Overall 439 pts had pts with RAS WT/BRAF WT mCRC. Progression-free (PFS) and overall survival (OS) were longer for pmab + FOLFOX4 vs FOLFOX4 in both groups (Table). Results were similar when the ECOG = 1 definition was used (Cytoreduction Group: non-LLD and asymptomatic. Tumour-related symptoms were defined as an EQ-5D pain/discomfort scale score $>$1 at baseline or an Eastern Cooperative Oncology Group score of 1.

Table: 481P

<table>
<thead>
<tr>
<th>Items</th>
<th>TRG 0 (N = 77)</th>
<th>TRG 1 (N = 143)</th>
<th>TRG 2 (N = 156)</th>
<th>TRG 3 (N = 71)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvested lymph nodes (median)</td>
<td>8</td>
<td>10</td>
<td>11</td>
<td>13</td>
<td>0.001</td>
</tr>
<tr>
<td>LN metastasis (6.6%)</td>
<td>6/7.8</td>
<td>21/14.7</td>
<td>34/21.8</td>
<td>27/38.3</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td>Extraneural TD (6.6%)</td>
<td>3/3.9</td>
<td>11/7.7</td>
<td>25/16.0</td>
<td>15/21.1</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Conclusions: The number of patients with RAS wild-type (WT) or BRAF WT metastatic colorectal cancer (mCRC) who are candidates for disease control. Results were similar when the ECOG = 1 definition was used (Cytoreduction Group: non-LLD and asymptomatic. Tumour-related symptoms were defined as an EQ-5D pain/discomfort scale score $>$1 at baseline or an Eastern Cooperative Oncology Group score of 1.

Results: Overall 439 pts had RAS WT/BRAF WT mCRC. Progression-free (PFS) and overall survival (OS) were longer for pmab + FOLFOX4 vs FOLFOX4 in both groups (Table). Results were similar when the ECOG = 1 definition was used (Cytoreduction Group: non-LLD and asymptomatic. Tumour-related symptoms were defined as an EQ-5D pain/discomfort scale score $>$1 at baseline or an Eastern Cooperative Oncology Group score of 1.

Table: 482P

<table>
<thead>
<tr>
<th>Median, months</th>
<th>PFS</th>
<th>OS</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytoreduction Group (n = 252)</td>
<td>11.0</td>
<td>23.8</td>
<td>0.77 (0.68-0.86)</td>
</tr>
<tr>
<td>Pmb + FOLFOX4</td>
<td>10.0</td>
<td>23.8</td>
<td>0.77 (0.68-0.86)</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>9.3</td>
<td>20.2</td>
<td>0.78 (0.60-1.03)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.36-1.00</td>
<td>0.78 (0.60-1.03)</td>
<td></td>
</tr>
<tr>
<td>Control Group (n = 172)</td>
<td>9.9</td>
<td>24.0</td>
<td>0.68 (0.49-0.94)</td>
</tr>
<tr>
<td>Pmb + FOLFOX4</td>
<td>12.9</td>
<td>31.1</td>
<td>0.68 (0.49-0.94)</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>9.9</td>
<td>24.0</td>
<td>0.62 (0.44-0.88)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.68 (0.49-0.94)</td>
<td>0.62 (0.44-0.88)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence intervals

Conclusions: Although the definition of tumour-related symptoms used in this study has some limitations, this exploratory analysis suggests that first-line pmab + FOLFOX4 treatment significantly improves PFS and OS vs FOLFOX4 alone in pts with RAS WT/BRAF WT mCRC who are candidates for disease control.

Clinical trial identification: NCT0364013

Legal entity responsible for the study: Amgen

Funding: Amgen (Europe) GmbH

Disclosure: J. Taieb: Honoraria/consulting/advisory role for Roche, Amgen, Merck, Lilly, Sanofi, Celgene, Sirtex. M. Peeters: Received research funding and acted in consultancy/advisory roles for Amgen and received research funding and participated in symposia for Merck Serono. S. Siena: Member of advisory boards or steering
Effect of 5 years of imaging and CEA follow-up to detect recurrence of colorectal cancer – PRODIGE 13 a FCFD and Unicancer phase III trial: baseline characteristics

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Background: For colorectal liver metastasis (CRLM), surgical resection is now established as the standard treatment option. The recent advance of anti-cancer drugs including the molecular-targeted agents enables us to extend the surgical indication and improve prognosis in a case with advanced CRLM. Because mFOLFOX with cetuximab has been expected to provide early tumor shrinkage for advanced-stage CRLM with KRAS wild type, we conducted this phase II trial to prospectively evaluate the significance of the treatment strategy.

Methods: Patients having advanced CRLM (tumor number > 5 and/or technically unresectable) with KRAS wild were included to this study. First, mFOLFOX with cetuximab was induced, and surgical indication was evaluated every 4 cycles (2 months). If all tumors including primary tumor became regarded as technically resectable, we performed surgical resection after the waiting period of 1 month. If they were unresectable, we repeated the regimen within the upper limit of 12 cycles. The primary endpoint was R0 resection rate. The secondary endpoints included safety, PFS, and OS.

Results: Between May 2012 and May 2015, total 50 patients were enrolled to this trial in 14 centers. The induction was not done in 2 patients, who were excluded. The median age of the 48 patients was 62.5 (range: 45 to 79) including 36 men and 12 women. The median tumor number detected by CT before the induction was 12 (1 to 57). Although the experimental treatment was incomplete in 15 patients, the rates of complete and partial response were 6% and 43.6%, respectively. R0 and R1 resections were done with no mortality in 26 and 5 patients, respectively (R0 resection rate: 54.2%), whereas surgery was abandoned in 2. Under the median follow-up of 1.5 years, the 1-year PFS was 51.7%, and 2-year OS was 71.3%.

Conclusions: For advanced CRLM with KRAS wild, mFOLFOX with cetuximab induction therapy was safely done and provided the sufficient R0 resection rate. This strategy can be effective to improve prognosis, which will be evaluated by further follow-up.

Clinical trial identification: UMIN Clinical Trials Registry, C00007923

Legal entity responsible for the study: The Institutions Review Board of each participating institutions

Funding: Self-funding

Disclosure: All authors have declared no conflicts of interest.

Impact of depth of response (DpR) on survival in patients (pts) with RAS wild-type (WT) metastatic colorectal cancer (mCRC) receiving first-line panitumumab + FOLFOX4 vs FOLFOX4

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Background: DpR has been associated with overall survival (OS) in first-line trials of epidermal growth factor receptor inhibitors + chemotherapy in pts with mCRC. Here
we evaluate the impact of DpR on progression-free survival (PFS) and OS in pts with RAS WT mCRC from the PRIME trial.

Methods: PRIME (NCT00364601) was a randomised, phase III trial of first-line panitumumab + FOLFOX4 vs FOLFOX4 in pts with mCRC. DpR was calculated as the maximal % change from baseline to nadir in pts who had tumour shrinkage. In pts with tumour growth, DpR was defined as 0%. In these exploratory analyses, the impact of DpR on survival was evaluated both as a continuous and ordinal variable (using 5 categories based on 8 DpR) in simple and multiple Cox regression models. The multiple Cox regression model also included terms for treatment and stratification factors (baseline ECOG score and region).

Results: Overall, 460 pts with RAS < /SSF > WT mCRC who had measurable disease at baseline and calculable DpR post-baseline, were included in the analysis. Median DpR was higher in pts receiving panitumumab + FOLFOX4 vs FOLFOX4 (54% vs 46%, p = 0.0149). In the simple regression model, DpR was associated with PFS (p < 0.0001) and OS (p < 0.0001) irrespective of treatment received. Overall results by DpR category are shown in the Table. DpR remained associated with PFS (p < 0.0001) and OS (p < 0.0001) in the multiple Cox regression model.

Table: 485P

<table>
<thead>
<tr>
<th>Group</th>
<th>DpR%</th>
<th>Median, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-35</td>
<td>2.1 5.8 11.1 11.2 17.7</td>
</tr>
<tr>
<td>2</td>
<td>35-54</td>
<td>4.08 (0.36, 8.49)</td>
</tr>
<tr>
<td>3</td>
<td>54-71</td>
<td>0.63 (0.33, 0.59)</td>
</tr>
<tr>
<td>4</td>
<td>71-100</td>
<td>0.44 (0.21, 0.18)</td>
</tr>
</tbody>
</table>

*Group HR compared with Group 2, continuous HR estimate is for the hazard ratio associated with a 1% difference in DpR, *p < 0.0001.

Conclusions: These exploratory analyses from PRIME suggest that deeper responses are significantly associated with longer OS and PFS in pts with RAS WT mCRC.

Clinical trial identification: NCT003646013

Legal entity responsible for the study: Amgen

Funding: Amgen (Europe) GmbH

Disclosure: S. Siena: Member of advisory boards or steering committees or principal investigator for Amgen, Bayer, Boehringer Ingelheim, Celgene, Genentech, Ignyta, Merck, Merrimack, Novartis, Pfizer, Roche, and SanofiAventis. F. Rivera Herrera: Acted on advisory boards and received research funding from Amgen, Sanofi, Merck-Serono and Roche. J-Y. Douillard: Honoraria/travel/accommodation/expenses while Merck, Merrck, Lilly, Sanofi, Celgene, Sirtex R. Kovalakis: Employee of Amgen Ltd and stockholder. M. Demongy: Employee of Amgen (Europe) GmbH and stockholder. M. Peeters: Received research funding and acted in consultancy/advisory roles for Amgen and received research funding and participated in symposia for Merck Serono.

486P Brain metastasis in advanced colorectal cancer: Results from the South Australian metastastic colorectal cancer (SAmCRC) registry


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Background: The SAmCRC registry has been enrolling patients since February 2006. Patterns of care have evolved leading to longer survival. Brain metastasis is considered significantly associated with longer OS and PFS in pts with mCRC and survival imaging does not routinely include the brain. The reported rate ranges from 6.6% to 3.2%. We have analysed the SAmCRC registry to assess the frequency of brain metastasis in the SA population and the timing of presentation, which may guide the timing of appropriate surveillance assessments.

Methods: The SAmCRC registry was analysed to assess the number of patients presenting with brain metastasis during their lifetime. Patient characteristics are reported and overall survival was analysed using the K-M method.

Results: 4100 patients have been entered into the registry between 2/2006 to 12/2015. The median age for all patients is 70.8 (17.2-104.83), 43% female & where available 42% are KRAS exon 2 MT. Only 59 patients developed brain metastasis (1.4%). The clinical characteristics of those with brain metastasis are as follows; median age 65.3 yrs (range 37-87 yrs), 51% were female. Site of primary 34% lung, 36% left, 29% right, site of metastasis at presentation; 47% liver, 54% lung, 7% bone and 13.6% brain. Where KRAS was known, 55% had KRAS exon 2 MT. Prior surgery for metastatic disease; liver = 15 (25%), lung = 5 (8%), prior lines of chemotherapy (median 2, range 0-4). The median time to diagnosis of brain metastasis was 1.9 yrs (range 0-6 yrs). Thirty one (53%) had craniotomy performed and 93% had whole brain radiotherapy. The median survival from diagnosis of brain metastasis was 4.2 months (95CI 2.9-5.5). If brain metastasis at initial diagnosis of mCRC are excluded, (n = 53) the median time to CNS metastasis is 2.05 years (range 0.3-6) and median survival is 3.8 months (95CI 2.0-5.7).

Conclusions: Results in a population setting confirm that brain metastasis are rare (1.4%) and the median time to development is 1.9 yrs. Patients with brain metastasis are younger, more likely female and KRAS MT which may allow patient selection for inclusion of CT Head imaging. Clinicians should be mindful of including imaging of brain in their surveillance protocol given the potential for surgical resection and stereotactic radiotherapy techniques.

Clinical trial identification: N/A

Legal entity responsible for the study: Flinders University

Funding: Flinders University, Haematology Oncology Unit.TQEH

Disclosure: All authors have declared no conflicts of interest.

Survival after resection of colorectal cancer with synchronous metastases – a Danish population based historic cohort study

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Background: Conflicting data exist on the optimal treatment for resectable synchronous metastatic disease in liver and/or lungs in patients with colorectal cancer (CRC). We examined the long term survival of a large national cohort of patients resected for CRC and timing of treatment for synchronous metastasectomies.

Methods: From 2000-2013 we included all patients from the Danish Cancer Registry and the Danish National Patient Registry recorded with CRC surgery and adenoecarcinoma. We also obtained data from the Danish National Patient Registry for patients operated for liver and/or lung metastases synchronously (<90days) from the date of CRC surgery.

Results: A total of 35,993 patients had surgery for colon (n = 24,206) (46.4% females (n = 16,711) and 53.6% males (n = 19,282)). 2,625 patients (7.3%) were surgically treated for synchronous metastatic disease with liver and/or lung surgery. 117 patients (0.3%) had liver surgery prior to CRC surgery while 1,458 patients (4.1%) underwent liver surgery following resection of the primary tumour. 106 patients (0.3%) were operated for lung metastases before and 944 patients (2.6%) after the CRC surgery. The 1 and 5 year overall survival for the entire cohort of patients were 84.1% (83.8%,84.4% and 56.7% (56.1%,57.3%) respectively. For the subset of patients undergoing synchronous metastasectomy the 1 and 5 year survival were 89.0% (85.3%,90.2%) and 41.4% (36.6%,45.9%).

Conclusions: We found a 5 year survival of 41.4% in patients treated for synchronous metastatic disease with liver and/or lung surgery.

Legal entity responsible for the study: Aarhus University Hospital

Funding: Aarhus University Hospital

Disclosure: All authors have declared no conflicts of interest.

Perioperative triplet chemotherapy plus bevacizumab (bev) in patients with borderline resectable colorectal cancer liver metastases (CLM): Preliminary safety and activity

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Background: Several end stage predictors of borderline resectability need to be included during neoadjuvant chemotherapy (NAC). Given the lack of prospective clinical trials, we performed a multi-center study on a real-world population of patients with resectable CLM. This is the first trial to select pathological response as primary endpoint.

Methods: According to Rubbia-Brandt et al., with a Simon 2-stage design (first step 22 pts; target 25 pts; overall 47 pts) and bev (5 mg/kg) day 1, oxaliplatin (85 mg/m²) day 2 and capecitabine 1000 mg/m² days 1-6; 4 cycles pre-operatively (the last without bev) and 4 cycles post-operatively (the last without bev).

Results: We present preliminary data on 36 pts (30 resected, 6 still awaiting). M/F: 21/15, median age 62 years (38-76), synchronous disease in 29 pts (80%), multiple nodules 61% (39% ≥ 4 nodules), N+ primary tumor 50%, CEA > 200, synchronicity. Limited resectable extrahepatic disease and in situ primary allowed. Primary endpoint: pathological response according to Rabeib Braund et al., with a Simon 2-stage design (first step 22 pts; target 45 pts; overall 67 pts) and bev (5 mg/kg) day 1, oxaliplatin (85 mg/m²) day 2 and capecitabine 1000 mg/m² day 1, 2, 3, 4, 5 cycles pre-operatively (the last without bev) and 4 cycles post-operatively.

Conclusions: COI-B regimen is a feasible perioperative chemotherapy for borderline resectable CLM. This is the first trial to select pathological response as primary endpoint with encouraging activity.

Legal entity responsible for the study: N/A

Funding: Istituto Nazionale Tumori

Disclosure: All authors have declared no conflicts of interest.

Phase 2 of intra-arterial hepatic (IAH) bevacizumab with systemic chemotherapy (CT) in second line treatment of liver metastases of colorectal cancer (LMCRC)

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Background: IAHCT is used in the treatment of LMRC. Regarding its anti-angiogenic effect bevaccuzum (B) is a good candidate for IAH treatment. This phase II evaluate IAH administration of B in second line treatment of LMRC combined with systemic treatment. We report here the results of the planned interim analysis on toxicity plus those on efficacy as the trial closed prematurely.

Methods: Inclusion criteria: patients (pts) with LMRC after failure to a 1st line of IV CT, ECOG performance status (PS) 0 or 1, at least one liver lesion evaluable by RECIST, extra-hepatic disease acceptable when limited to one or two lung metastases or lymph nodes potentially accessible to a curative treatment. They had to receive IAH treatment with B, 7.5 mg/kg every 4 weeks, and systemic CT with capecitabine (2 g/m² day 14) (d 14) followed by 7 days rest and oxaliplatin (200 mg/m²) every 21d) or oxaliplatin (130 mg/m² every 21 d) depending on the 1st line received.

Results: Between 08/2013 and 02/2015, 16 pts from 5 centers were included: 6 men, 4 women (median age 61 years); ECOG PS0 (7) and PS1 (3); limited extra-hepatic disease in 4 pts. Median duration of 1st line treatment was 6 months. IAH catheter was implanted surgically in one pt and radiologically in 9 pts. Pts had an average of 6 cycles of IAH B, >1 received oxaliplatin and 7 irinotecan concomitantly. There was one grade (G) 3 allergic reaction to IAH B, one G3 abdominal pain, one G3 mucusitis, one G3 nausea and one G3 vomiting events. Related to the use of B, 2 G3 thromboembolic events and 3 G3 hypertension were observed. The arterial catheter has to be replaced in one pt and a thrombosis of hepatic artery was observed in a second one preventing continuation of IAH treatment after one cycle. In the 9 evaluable pts, 2 had partial response (22%), 5 stable disease (56%) and 2 progressive disease (22%). The median progression-free and overall survival were 5.2 months 95%CI [1.6 – 6.2] and 13.5 months [4.8 – NR].

Conclusions: IAH administration of bevacizumab in pts with LMRC seems to be feasible with no major side effect. The efficacy reported did not suggest a major effect of this treatment that should rather be used in combination with IAHCT with oxaliplatin.

Legal entity responsible for the study: Gustave Roussy, Villejuif, France

Funding: Programme Hospitalier de Recherche Clinique

Disclosure: M.P. Ducrêux: Receipt of grants/research supports: Roche, Chugui, Pfizer. Receipt of honoraria for jobs: Roche, Celgene, Merck Serono, Amgen, Novartis, Sanofi, Pfizer, Lilly. Sponsor: Head of Business Unit, Sandorf. V. Boige: Advisory boards: Bayer, Symposium participation: Bayer, Amgen. D. Malka: Symposium participations: Roche, Amgen, Lilly, Merck Serono, Research funding: Merck-Serono, Roche, Amgen Advisory boards: Roche, Amgen. All other authors have declared no conflicts of interest.

Clinical trial identification: ClinicalTrials.gov: NCT01677884

Clinical trial identification: ClinicalTrials.gov: NCT02086636

Legal entity responsible for the study: A/ N/A

Funding: Istituto Nazionale Tumori

Disclosure: All authors have declared no conflicts of interest.
Impact of surgical resection of liver metastases on outcome of patients with KRAS-wildtype exon 2 (KRAS-wt) metastatic colorectal cancer (mCRC) treated with a cetuximab-based first-line therapy - Interim analysis of the German non-interventional study ERBITAG

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Background: Cetuximab in combination with irinotecan- or oxaliplatin-based chemotherapy (CT) has shown to increase among other efficacy parameter the R0 resection rate of liver metastases (LM) of primary irresectable KRAS-wt mCRC patients (pts). The non-interventional study ERBITAG aimed to evaluate safety and efficacy of cetuximab in combination with various first-line CT regimens in pts with unresectable KRAS-wt mCRC.

Methods: KRAS-wt pts on a cetuximab-based first-line treatment with written informed consent could be enrolled in this prospective, non-interventional study. Primary endpoint was ORR, secondary endpoints were amongst others PFS, OS, TTF, and resection rate of liver metastasis. Here we update the interim analysis in terms of the outcome of pts according to secondary resection of LM.

Results: 456 KRAS-wt mCRC pts out of 817 recruited KRAS-wt pts were evaluable for this interim analysis. Location of metastasis was liver, lung, lymph nodes, and peritoneum in 70.6%, 23.5%, 22.4%, and 17.8% of pts, respectively. 39.7% of pts had liver-limited disease (LLD). 79.2% had surgery of the primary tumor and 15.6% had a secondary resection of LM, respectively. Resection of LM and/or lung metastases was done in 17.3% of pts, respectively. Resection of LM and/or lung metastases was done in 17.3% of pts, respectively. Resection of LM and/or lung metastases was done in 17.3% of pts, respectively. Resection of LM and/or lung metastases was done in 17.3% of pts, respectively. Resection of LM and/or lung metastases was done in 17.3% of pts, respectively.

Conclusions: Pts with resection of LM had a significant longer PFS and OS compared to pts without resection. Clinical trial identification: German Database on peri de of non-interventional trials NIS-Nr.: 114

Legal entity responsible for the study: Merck Serono GmbH, Darmstadt, Germany

Funding: Merck Serono GmbH, Darmstadt, Germany

Disclosure: U. Neumann: Honoraria - Amgen, Merck Serono, Roche; corporate-sponsored research - Merck Serono (Inst); C. Hering-Schubert: Honoraria - Amgen, Boehringer Ingelheim, Bristol-Myers Squibb; Celgene, Mundipharma, Novartis, Pfizer, Sanofi, Sandoz; stock ownership - Fresenius Medical Care, Merck KGaA honoraria - Fresenius Medical Care corporate sponsored research - Merck Serono (Inst); Roche (Inst); M.O. Zahn: Honoraria - Celgene consulting or advisory role Novartis; K.G. Steinbrügge: Employment - Merck Serono GmbH stock ownership - Merck KGaA; F. Ochsendorf: Honoraria - Merck Serono consulting or advisory role.

Background: Colorectal cancer remains one of the commonly diagnosed cancers. The liver is the most common site of metastatic disease and the majority of patients eventually die from cancer progression in the liver. We report on the South Australian experience of the use of liver directed treatment with SIRT and we analyze the safety and efficacy of this intervention.

Methods: Data was obtained from the State-wide Metastatic Colorectal Cancer Registry which was established in 2006. Patients treated with SIRT were identified. The objectives were to determine time to progression in the liver, overall survival, response rate, acute toxicity and safety of SIRT. 55 patients (37 males; 18 Females) were treated with SIRT from 2006-2015. The median age at disease was 67.9 years. 79% had ECOG score ≤ 2. 44 (80%) patients had liver limited disease; 11 (20%) had extra-hepatic disease. 4 (7%) patients had SIRT with first line chemotherapy; 22 (40%) had SIRT after ≥4 lines of chemotherapy; 10 (18.2%) received SIRT concurrent with chemotherapy; 45 (81.8%) had SIRT alone. Only 1 patient had SIRT twice.

Results: The median time to hepatic progression was 3.72 (95% CI: 2.26-4.83) months; the median survival was 10.6 (95% CI: 7.73-15.32) months. Patients with liver limited disease vs extra-hepatic disease showed no difference in median survival (14.2 vs 10.6 months, p = 0.967). In other unfavorable analyses, there was no significant difference in survival according to age, ECOG, lines of chemotherapy, number of liver lesions or presence of extra-hepatic disease. The radiological response rate was 14.2%. There was no grade 3 or 4 acute toxicity. The most common short-term adverse effects were hepatic pain (18%), nausea, vomiting and back pain. Data regarding potential long term toxicity was not systematically collected.

Conclusions: In this population based analysis, SIRT was mostly administered in pre-treated patients and we observed activity with an acceptable short term safety profile.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.
**A triplet combination with oxalipatin/capcitabine/irinotecan (XELOXIRI) plus cetuximab (Cmb) as a first-line treatment in wild-type KRAS, metastatic colorectal cancer: a dose escalating study**

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**Background:** We previously reported the promising activity of a twice-weekly oxalaplatin/capcitabine/irinotecan (XELOXIRI) plus bevacizumab, which was easier to administer than FOLFOXIRI/ bevacizumab, using capcitabine, instead of 5-fluorouracil, in pts with metastatic colorectal cancer (mCRC) (Cancer Chemother Pharmacol 2015). In order to achieve more potent efficacy, we explored the dose limiting toxicity and feasibility of the combination XELOXIRI plus cetuximab (XELOXIRI/Cmb) in pts with KRAS wild type mCRC.

**Methods:** Pts were eligible if they had KRAS wild-type mCRC (liver and/or other metastasis), ECOG PS 0-1, were either negative or heterozygous for UGT1A1*6 or UGT1A1*28 and were not pretreated for metastatic disease. Treatment consisted of oxalplatin (100 mg/m² day 1), capcitabine (1700 mg/m²/day from day 2 to 15), irinotecan (100-120,150 mg/m² for dose levels 1, 2, or 3) day 1) repeated every 3 weeks and weekly cetuximab (400 mg/m² and, thereafter, 250 mg/m², day 1). The dose of irinotecan was escalated if dose limiting toxicities (DLT) were absent in the first three pts per cohort, or if ≤2 DLTs were observed in six pts. If the MTD was not reached at the planned dose levels, the RD of irinotecan was defined as 150 mg/m², which is the maximum dosage approved use in Japan.

**Results:** From Oct. 2012 to Dec. 2014, 12 pts (F/M: 5/7, median age: 64.5 years, PS 0/1: 11/1) received a median of 6 cycles of chemotherapy (range 2-10). The DLT was Grade 4 neutropenia, which was observed in 1 of 6 patients at dose level 2. MTD was not reached at dose level 3. Therefore, the RD of irinotecan was defined as 150 mg/m². Most common grade ≥3 toxicities were neutropenia (49%), diarrhea (16.7%), and febrile neutropenia (8.3 %). The response rate was 83.3% (CR: 1 pt and PR: 9 pts), including 4 conversion cases. At a median follow-up of 18.7 months, median PFS was 14.5 months and median OS was not yet reached.

**Conclusions:** The combination of XELOXIRI and cetuximab is feasible and has an acceptable toxicity profile; neutropenia was the DLT; recommended dose of irinotecan is 150 mg/m². The observed response rate of 83.3% is very promising and warrants further investigation.

**Clinical trial identification:** Trial protocol number (UMIN000009144) release date (2012/10/18)

**Legal entity responsible for the study:** Sapporo Medical University School of Medicine

**Funding:** Sapporo Medical University School of Medicine

**Disclosure:** All authors have declared no conflicts of interest.
Phase II trial of panitumumab monotherapy for patients with KRAS exon2 wild type colorectal cancer after progression on cetuximab. HGSSG1101


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Background: Both panitumumab and cetuximab known as antibody to EGFR play a key role in treatment with patients for colorectal cancer. Although the action for EGFR is considered to be similar in clinical practice, the differences between these drugs have been reported. The affinity for EGFR shows to be higher in panitumumab. And because of different subclass of antibody between panitumumab [IgG2] and cetuximab [IgG1], it has been reported that cetuximab has Antibody-dependent cellular cytotoxicity (ADCC). Some retrospective analyses have revealed that the administration of panitumumab after cetuximab demonstrated the valuable efficacy, however, the prospective study for cetuximab refractory patients have only been a few reported.

Methods: HGSSG1101 is a multicenter phase II study. Eligibility includes histologically confirmed KRAS exon2 colorectal cancer, previously received oxaliplatin/irinotecan/fluoropyrimidine, and previously refractory for cetuximab. Patients intravenously received panitumumab 6 mg/kg every 14 days. The primary endpoint was 6-month progression-free survival rate (threshold 8%, expected 31%) and the secondary endpoints were safety, response rate, disease control rate, PFS and OS. We estimated that a target sample size of 28 patients.

Results: Between May 2011 and April 2014, 33 pts were enrolled. Two patients were ineligible. Patients characteristics were as follows: median age 67 years (range 44-90), male: female 23:8, PS 0:1:2 17:13:1, best response for cetuximab PR:SD:PD 8:15:5.

 Patients with a secondary metastases resection survived 50.5 months, patients without a secondary metastases resection 24.8 months (p < 0.0001). Patients who were treated with panitumumab and had received metastases resection survived 54.5 months.

Conclusions: The median overall survival of 25.0 months from the start of the 1st-line therapy reflects the target treatment of the colorectal carcino in the practices. With a secondary metastases resection had a significantly prolonged overall survival.

Clinical trial identification: The ONCOreg register study is listed since 04/26/2013 in the German Clinical Trials Register under the following number: DRKS00004818

Disclosure: All authors have declared no conflicts of interest.
Efficacy of first-line modified FOLFOX6 with panitumumab or bevacizumab in RAS wild-type/BRAF wild-type metastatic colorectal cancer: impact of tumour symptoms and extent of disease

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Background: In patients with previously untreated metastatic colorectal cancer (mCRC), the goal of treatment is likely to influence choice of first-line therapy, as suggested in ESOM 2016 guidelines previewed at WOCR 2015. We conducted an exploratory analysis of the efficacy of first-line modified FOLFOX6 (mFOLFOX6) plus panitumumab or bevacizumab in patients with RAS wild-type (WT)/BRAF WT mCRC based on the aim of treatment: cytoreduction or disease control.

Methods: PEACT (NCT00819780) was an open-label randomised phase II trial of first-line panitumumab + mFOLFOX6 vs bevacizumab + mFOLFOX6. Using baseline characteristics, patients with RAS WT/BRAF WT mCRC were retrospectively classified into groups according to treatment goal: Cytoreduction group (liver-limited disease [LLD] and/or symptoms) or Disease-control group (asymptomatic with non-liver-limited metastases [with or without liver metastases]). Patients with an Eastern Cooperative Oncology Group (ECOG) score of 1 were considered to have tumour-related symptoms.

Results: The analysis included 155 patients with RAS WT/BRAF WT mCRC, of whom 83 were in the Cytoreduction group and 72 were in the Disease-control group. Median PFS and OS were numerically longer with panitumumab + mFOLFOX6 vs bevacizumab + mFOLFOX6 in both groups (Table).
Background:Generic drugs represent a relevant, potential opportunity in terms of cost savings. However, several physicians are uncomfortable with the replacement of the branded drugs with generic equivalents, indicating among several reasons their hypothetical lower tolerability.

Methods:In the preclinical phase we in vitro tested the concentrations, stability and efficacy in CACO-2 cell line of branded versus generic oxaliplatin formulations. In a second step we retrospectively collected safety and toxicity data from 427 colorectal cancer patients submitted to an oxaliplatin-based regimen between January 1994 and June 2014 at our institution. Patients were stratified according whether they received branded (BRAND group) or generic oxaliplatin (GENERIC group). Primary aim of this second step was the assessment of the hypersensitivity reaction (HSR) incidence. Secondary aims were the evaluation of hematological and non-hematological toxicities and, in metastatic patients, clinical outcomes.

Results:Preclinical tests did not demonstrated differences in concentration and stability in distinct storing conditions between branded and generic formulations. Furthermore, dose- and time-dependent anti-proliferative activities were similar. The incidence of HSRS was 12.1% in BRAND (333/2737 patients) and 9.8% (151/1548) in GENERIC group (p = 0.46). Occurrence of grade II-IV HSRS and severe HSRS leading to oxaliplatin discontinuation were comparable. In metastatic patients no significant difference in response rate was reported. A longer PFS was recorded in the BRAND group (14.4 vs 12.4 months, log rank p < 0.03), whereas OSs were comparable (24.9 vs 26.9 months, log rank p = 0.14).

Conclusions:Tested generic and branded oxaliplatin formulations had equivalent concentrations of the active drug, and presented similar stability and in vitro efficacy. Likewise, the incidence of oxaliplatin-induced HSRS as well as toxicity profiles and clinical outcomes were similar. According to our data, generic oxaliplatin can be considered a safe and active alternative to the branded formulation.

Legal entity responsible for the study:AUO San Luigi Gonzaga

Funding:AUO San Luigi Gonzaga

Disclosure:All authors have declared no conflicts of interest.

A 12-week regimen with interdigitating FOLFOX/bevacizumab and pelvic chemoradiation for synchronous primary and metastatic rectal cancer. The CHROME B trial

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Background:Chemotherapy used during chemoradiation for advanced rectal cancer is inadequate for tumour control or tumour eradication. The aim of this study was to assess tolerability and local/systemic control of a new regimen adding irinotecan to oxaliplatin, bevacizumab and radiotherapy.

Methods:This was a single arm prospective trial for patients presenting with untreated synchronous symptomatic primary and metastatic rectal cancer. The treatment regimen was 12 weeks long. FOLFOX chemotherapy comprised oxaliplatin (Oxa) 100 mg/m² day 1, leucovorin 200 mg/m² day 1, 5-FU 400 mg/m² bolus day 1, then 5-FU 225 mg/m² day 2 and 5-FU/continuous infusion 200 mg/m²/day) given in week 1, 6, and 11. Pelvic radiotherapy (25.2 Gy in 3 weeks in 1.8 Gy/fr with concurrent Ox 85 mg/m² day 1 and 5-FU/continuous infusion 200 mg/m²/day) given in week 3-5, and week 8-14. Bev 5 mg/kg was given in week 1, 3, 5, 7, 9, 11. In total patients received in 12 weeks, 3 courses of FOLFOX, 50.4 Gy with Ox3+FU, and 2-weekly Bev. All patients were staged with CT, MRI and FDG-PET before and 4 weeks after treatment.

Results:Thirty patients were treated in this trial. The median age was 58 (range 36-75) years. 56.7% were male. Rectal primary MRI stage was T2 3%, T3 73% and T4 24%. Liver metastasis was present in 80%. 33% had more than one site of metastasis. 24 patients (80% [80% CI 68%-89%]) reached week 12 of the treatment. Chemotherapy dose modification was required in 63%, mainly for haematologic toxicity (neutropenia G4 23%, G3 23%, febrile neutropenia G3 3%, thrombocytopenia G4 3%). PET (SUV) response 4 weeks post-therapy for pelvic disease was CR + PR 100% [95% CI 98%-100%] (CR14%), and for distant disease was CR + PR 93% [95% CI 76%-99%] (CR 41%). At 24 months, freedom from failure for pelvic and distant disease were 86% [95%CI 75%-100%] and 28% [95% CI 15%-50%] respectively. Overall survival at 24 months was 95% (95% CL 52%-86%).

Conclusions:It is feasible to deliver interdigitating intensive chemotherapy with bevacizumab and radiotherapy to treat primary and metastatic rectal cancer simultaneously. Favourable tumour control rates are encouraging. This treatment design warrants further investigation.
metastases were predictive of better PFS (HR 0.39; 95% CI: 0.16–0.97, p = 0.04) and worse OS (HR 2.25; 95% CI: 1.25–4.03, p = 0.01), respectively.

Conclusions: This is the second largest series of advanced AC ever reported. Doublet CT with PF and PTX-based CT are active regimens in this setting. Prospective clinical trials are needed to standardize treatment pathways, investigate the potential of novel therapeutics and ultimately improve the modest survival outcome of this pt population.

Legal entity responsible for the study: The Royal Marsden NHS Foundation Trust

Funding: The National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at the Royal Marsden NHS Foundation Trust and Institute of Cancer Research

Disclosure: I. Chau: Advisory roles with Merck Serono, Roche, Sanofi Oncology, Bristol Myers Squibb, Eli-Lilly, Novartis, Gilead Science. Research funding from Merck Serono, Novartis, Roche and Sanofi Oncology: Honoraria from Roche, Sanofi Oncology, Eli-Lilly, Taiho. D. Cunningham: Research funding from: Roche, Amgen, Celgene, Sanofi, Merck Serono, Novartis, AstraZeneca, Bayer, Merrimack and MedImmune. All other authors have declared no conflicts of interest.

Background: In the phase 3 randomized CORRECT trial, REG improved survival vs placebo in treatment-refractory mCRC; 19% of REG-treated patients had PFS >4 m. In this exploratory analysis, the impact of baseline factors on PFS and response was assessed in patients with mCRC who received REG 160 mg QD for 3 wks then as multiple doses in 28-day cycles (3 weeks on/1 week off). The proportion of patients with better performance status, with no liver involvement, and a longer time since diagnosis of metastatic disease (Table 506P) was higher in the long PFS group than in the short PFS group. The best response observed was stable disease in 15/21 (71%) patients. The most common drug-related AEs (long PFS, short PFS) were hypertension (20%, 14%), fatigue (13%, 13%), diarrhea (8%, 4%) and hypophosphatemia (8%, 4%).

Conclusions: This exploratory analysis suggests that among patients with mCRC treated with regorafenib, the long PFS (>4 months) subgroup tended to have a higher proportion of patients with better performance status, with no liver involvement, and a longer time since diagnosis of metastatic disease. Higher rates of some AEs and dose reductions in the long PFS group may be related to longer treatment duration.

Clinical trial identification: NCT01538680

Legal entity responsible for the study: Bayer

Funding: Bayer


Background: REG is an oral multikinase inhibitor used for the treatment of metastatic CRC and advanced GIST. This phase 1 study was designed to evaluate the PK and safety of REG in cancer patients with severe renal impairment (SRI; creatinine clearance (CLcr) <15 to <30 mL/min) vs a control (CTR) group with normal or mildly impaired renal function (CLcr 15 to ≥30 mL/min).

Methods: This was a phase 1, open-label, non-randomized, 2-parallel group study in patients with advanced solid tumors with severe vs normal/mild renal impairment (NCT01853046). REG 160 mg QD was administered as a single dose on Day 1 with a washout of 2-5 days, then as multiple doses in 28-day cycles (3 weeks on/1 week off). Antitumor activity was assessed according to RECIST v1.1 as a secondary endpoint. Blood samples were collected after single and multiple dose administrations for PK analysis. Adverse events (AEs) were graded according to NCI-CTCAE v4.0. Estimated CLcr was calculated using the Cockcroft–Gault equation.

Results: 24 patients (6 SRI and 18 CTR) were valid for PK and safety analyses. Doublets were for efficacy analysis. REG 160 mg QD was well tolerated and had an acceptable safety profile. The most common AEs were fatigue (80%), nausea (71%), and vomiting (71%). Antitumor activity was assessed according to RECIST v1.1 as a secondary endpoint. Blood samples were collected after single and multiple dose administrations for PK analysis. Adverse events (AEs) were graded according to NCI-CTCAE v4.0. Estimated CLcr was calculated using the Cockcroft–Gault equation.

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Cetuximab biweekly (q2w) plus mFOLFOX6 as 1st line therapy in patients (pts) with KRAS wild-type (wt) metastatic colorectal cancer (mCRC) - Primary endpoint and subgroup analysis of the CEBIFOX trial

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Background: The multicenter, single-arm, phase II trial (Simon’s two-stage design) evaluated the efficacy of mFOLFOX6 + cetuximab (500 mg/m2) q2w as 1st line therapy in KRAS wt mCRC. Final extended molecular and subgroup analyses are presented.

Methods: Primary endpoint was response rate (ORR) per RECIST 1.0 in stage 1 and 2, routinely assessed clinical parameters may help to identify patients with maximum likelihood of benefit from cetuximab-based chemotherapy. This study supports the efficacy and safety of q2w cetuximab given in combination with mFOLFOX6.

Conclusions: Despite minimal toxicity, there was no evidence to suggest any efficacy of cetuximab-based chemotherapy.
Phase II study of third-line cetuximab rechallenge in patients with metastatic wild-type K-RAS colorectal cancer who achieved a clinical benefit in response to first-line cetuximab plus chemotherapy (JACCRO CG-08)


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Background: Cetuximab rechallenge has been reported to be promising (Santini D et al. Ann Oncol 2012). We performed a multicenter phase II prospective study in Japan.

Methods: The study cohort comprised patients with metastatic wild-type K-RAS colorectal cancer who achieved a confirmed clinical benefit at first-line therapy (confirmed stable disease for at least 6 months or clinical response) in response to first-line cetuximab plus chemotherapy, then had disease progression and received second-line chemotherapy, and finally had a third-line chemotherapy with cetuximab (400 mg/m2 as an initial dose followed by 250 mg/m2 monthly). The primary endpoint was the 3-month progression-free rate. The sample size was estimated to be at least 30 patients, assuming a 3-month progression-free rate of 15% based on null hypothesis versus a 3-month progression-free rate of more than 35% as the alternative hypothesis, with a power of 0.80, and an alpha value of 0.05.

Results: A total of 36 patients were recruited. Two patients were excluded: one met the ineligibility criteria, and the other did not receive the study treatment because of poor condition at the time scheduled for treatment. The 3-month progression-free rate of 44.1% (95% confidence interval: 27.4-60.8) met the primary endpoint, with a median progression-free survival time of 2.4 months and an overall survival time of 9.1 months. The overall response rate and disease-control rate were 2.9% and 55.9%, respectively. The most frequent grade 3 to 4 adverse events were neutropenia (28.6%), skin toxicities occurred in 80% of all patients, as expected.

Conclusions: Third-line cetuximab rechallenge may be clinically beneficial comparable to regorafenib and TAS102, with manageable toxicity.

Clinical trial identification: Trial protocol number: UMIN000016038 UMIN release date: 2013/07

Legal entity responsible for the study: Akitoshi Tsuji

Funding: Japan Clinical Cancer Research Organization


Adherence to guidelines for colorectal cancer prevention and its relationship to this cancer in the Basque country: a case-control study


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Background: The European Prospective Investigation into Cancer and Nutrition (EPIC) has designed an index score based on recommendations for cancer prevention of the World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR). We aimed to investigate whether concordance with the specific guidelines for colorectal (CRC) prevention was related to this cancer in an adult population of the Basque Country.

Methods: The present study included 310 cases and 310 controls randomly selected, all of them participants from the CRC screening program in the Basque Country (Spain), aged 50–69 years. At recruitment, dietary, anthropometric, and lifestyle information was collected through a questionnaire. A score was constructed based on the WCRF/AICR recommendations (2007) and the convincing evidences of association between lifestyle factors and CRC (WCRF/AICR, 2011). The recommendations used for the construction of the score were: physical activity (PA), dietary fibre, red meat and processed meat, alcohol drinks and body fatness. The total score range was 0 to 5. Higher scores indicated greater concordance with recommendations. All analyses were conducted on SPSS v. 22.0.

Results: The mean score (2.7) was similar for cases and controls (2.7 ± 0.2). The scores for dietary fibre were higher in controls (0.60 ± 0.33) than in cases (0.50 ± 0.33) (P = 0.013), whereas the scores for PA were higher in cases (2.0 ± 0.33) than in controls (1.4 ± 0.33) (P < 0.001). For the rest of components no significant associations were observed with CRC: red meat and processed meat (z = 0.65, P > 0.05), alcoholics (z = 0.80, P > 0.05) and body fatness (z = -0.52, P > 0.05).

Conclusions: The results of this study suggest that following the recommendations on dietary fibre for cancer prevention could be associated with a lower risk of CRC in this population. The differences in PA scores could be due to lifestyle changes after the diagnosis. More research is needed to elucidate the potential lifestyle risk factors for CRC and how modification of these lifestyle factors could prevent it.

Legal entity responsible for the study: Dr. Marta Arroyo-Izaga

Funding: Department of Health, Basque Country Government (2011111153) and SAIOEK (S-PET1UN00508, a pre-doctoral grant from the Basque Government (PRE_2013_2_3884)

Disclosure: All authors have declared no conflicts of interest.

Compassionate use program for trifluridine/tipiracil (TAS-102) in metastatic colorectal cancer: a real-life overview

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Background: Compassionate use programs (CUPs) provide a treatment option for appropriate patients with unmet medical needs. We describe the trifluridine/tipiracil (TAS-102) CUP set up prior to marketing authorization for management of pretreated metastatic colorectal cancer (mCRC) in countries outside the USA and Japan.

Methods: Registration gave mCRC patients (pts) early access to 2 cycles of treatment, renewable as necessary. Pts’ characteristics were collected at registration.

Results: A total of 879 pts were registered in 21 countries by the 1st April 2016 cutoff (Argentina, Brazil, Australia, Austria, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Spain, The Netherlands, Portugal, UK, United States of America, Uruguay, Venezuela).
Pharmacokinetic and pharmacodynamic (PK/PD) analysis results from the phase 3 RECURse trial of trifluridine and tipiracil (TAS-102) versus placebo (pbo) in patients (pts) with refractory metastatic colorectal cancer (mCRC)


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Background: The efficacy and safety of TAS-102, an oral agent that combines trifluridine and tipiracil (FTD/TPI), in pts with mCRC refractory/intolerant to standard therapy was evaluated. This study aimed to explore the relation between exposure and treatment (Tx) responses.

Methods: Three blood samples were collected at steady state in Cycle 1 at 1, 3, and 6 hours after pts received 35 mg/m² of FTD/TPI or placebo in the morning. Pts were stratified by prior treatment lines of prior treatment for metastatic disease (28%, 32%, and 32%, respectively); 4% had received 1 line of treatment and 4% unknown. The main reasons for not initiating treatment included cancellation of request due to worsening condition and progressive disease. 37 pts (4%) permanently discontinued treatment before the end of cycle 1 or 2 due to disease progression (19 pts), death (8 pts), or other reasons (10 pts). A total of 184 pts (25% of pts in cycles 1 or 2) went on to receive trifluridine/tipiracil for cycles 3 or 4. Of those, 28 pts had a dose reduction due to neutropenia (17 pts), diarrhea (3 pts), or other adverse events (8 pts; vomiting, drowsiness, creatinine increase, bowel obstruction, pleural effusion). 24 pts (3%) had treatment permanently discontinued before end of cycles 3 or 4 due to progressive disease. 20 pts went on to receive treatment in cycles 5 or 6, 16 pts with no dose reduction.

Results: Median OS, mo [95% CI] 8.9 [7.2, 10.2] 5.7 [4.0, 7.3] 9.2 [7.8, 11.1] 8.1 [5.3, 12.2] 0.72 [0.46, 1.11] 0.49 [0.32, 0.76] 0.60 [0.39, 0.92] 0.49 [0.32, 0.76] 0.26 [0.17, 0.40] 0.44 [0.29, 0.66] 0.60 [0.39, 0.92]

Any dose reduction, n (%) 22 (16) 0 16 (23) 6 (9) 2.67 [1.11, 6.41] NA NA 3.56 [1.30, 9.68] 2.67 [1.11, 6.41] 1.26 [0.50, 3.16] 0.44 [0.29, 0.66] 0.60 [0.39, 0.92]

Febrile neutropenia, n (%) 3 (2) 0 2 (3) 1 (1) 2.00 [0.19, 21.55] NA NA 1.26 [0.50, 3.16] 2.00 [0.19, 21.55] 1.26 [0.50, 3.16] 0.44 [0.29, 0.66] 0.60 [0.39, 0.92]

Table: 513P NA, not applicable. *Any delays that have occurred at Cycle 2 or later; denominators = number of pts who initiated Cycle 2 for each group
Background: The efficacy and safety of trifluridine/tipiracil (TAS-102) has been explored in patients with metastatic colorectal cancer (mCRC) refractory who were intolerant to standard therapies in the phase 3 RECOURSE trial. Treatment with trifluridine/tipiracil was associated with significantly improved overall and progression-free survival versus placebo. In a post hoc analysis, we compared the level of performance status (PS) at treatment discontinuation in the two arms.

Methods: PS was evaluated in RECOURSE using the Eastern Cooperative Oncology Group (ECOG) score. Patients included in this trial had PS = 0 or 1 at baseline. The PS at treatment discontinuation with ECOG scores 0 to 4 was compared to PS at baseline on treatment and placebo (descriptive statistics).

Results: A total of 759 patients (95% of the RECOURSE population) had information on treatment and placebo (descriptive statistics).

Table: S15P

<table>
<thead>
<tr>
<th>Baseline PS</th>
<th>Trifluridine/tipiracil</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0 (n = 278)</td>
<td>1 (n = 218)</td>
</tr>
<tr>
<td>PS at discontinuation</td>
<td>0</td>
<td>180 (65%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>78 (28%)</td>
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<tr>
<td></td>
<td>2</td>
<td>13 (5%)</td>
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<tr>
<td></td>
<td>3</td>
<td>6 (2%)</td>
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<td></td>
<td>4</td>
<td>1 (0.4%)</td>
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</table>

Conclusions: Our results indicate that, despite expected treatment-related adverse events, the level of PS at treatment progression was maintained in patients treated with trifluridine/tipiracil.

Legal entity responsible for the study: Taiho and Institut de Recherches Internationales Servier

Disclosure: All authors have declared no conflicts of interest.

Characteristics of patients (pts) with metastatic colorectal cancer (mCRC) treated with regorafenib (REG) who had progression-free survival (PFS) >4 months (m): Subgroup analysis of the phase 3 CORRECT trial

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Background: In CORRECT, REG significantly improved overall survival and PFS vs placebo in pts with treatment-refractory mCRC. We did a retrospective, exploratory subgroup analysis of REG-treated pts in CORRECT with PFS >4 m (long PFS) and ≤4 m (short PFS).

Methods: Pts with pretreated mCRC were randomized 2:1 to REG 160 mg or placebo QD for 3 weeks on/1 week off until disease progression, death, or unacceptable toxicity. PFS was the time from randomization to progression or death. Of 505 pts randomized to REG 98 (19%) had long PFS and 407 (81%) had short PFS.

Results: Compared to short PFS pts, the long PFS group had a higher proportion of patients with ECOG PS 0, 1–2 tumor sites, and ≥18 m since diagnosis of metastatic disease (Table). Long PFS pts received a median of 6 (1–12) cycles, short PFS pts a median of 2 (1–11). Mean actual daily doses were 138.7 mg (long PFS) and 149.2 mg (short PFS). Dose modifications occurred in 91% (long PFS) and 72% (short PFS). NCI-CTCAE (v3) grade (Gr) ≥1 REG-related treatment-emergent adverse events (TEAEs) occurred in 64% (long PFS) and 53% (short PFS). Most common REG-related Gr ≥3 TEAEs included increased bilirubin (8%, 13%), hypertension (17%, 5%), fatigue (13%, 9%), diarrhea (16%, 5%), rash/desquamation (3%, 6%), and hypophosphatemia (5%, 3%). Gr ≥3 laboratory toxicities (long PFS, short PFS) included increased bilirubin (8%, 13%), ALT (6%, 5%), and AST (5%, 6%). Although REG-related TEAEs led to a higher dose modification rate in long PFS pts (71% vs 52% for short PFS), discontinuations due to REG-related TEAEs were similar (long PFS 5%, short PFS 9%).

Conclusions: This exploratory analysis showed that pts with mCRC treated with REG who had PFS >4 m tended to have a better performance status, fewer metastatic tumor sites, and a longer time since diagnosis of metastatic disease, compared to pts with short PFS.

Clinical trial identification: NCT01103323

Legal entity responsible for the study: Bayer

Funding: Bayer

RESULTS: CTC counts before CRT were significantly higher than those after CRT (41.24 ± 18.45/5mL vs. 9.7 ± 8.9/5mL, P < 0.05). Based on TRG score, 67 patients were regrouped as 44 responders (TRG 3-4) and 23 non-responders (TRG 0-2). The CTC counts before CRT were not associated with tumor response. The CTC counts after CRT in responders (TRG 3-4) were significantly lower than non-responders (TRG 0-2) (5.93 ± 5.65/5mL vs. 16.65 ± 9.78/5mL, P < 0.05). The percentage difference of CTC counts (%CTC) between pre- and post-CRT were significantly higher in responders compared to non-responders (86.2% vs. 40.2%, P < 0.05). ROC (receiver-operating characteristics) analysis showed that %CTC was a stronger discriminator of treatment response (area under the curve of pre- vs. post-CRT CTC counts and %CTC of 0.83 and 0.88, respectively). Using 70.56% as the cut-off threshold for %CTC value, a higher accuracy of 88.06% (59/67) was obtained to discriminate responders from non-responders with a sensitivity of 93.18%, a specificity of 78.26%, a positive predictive value of 89.13% and a negative predictive value of 85.71%.

Conclusions: Circulating tumor cells are promising markers to predict tumor response after preoperative CRT for rectal cancer.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center

Funding: The National Natural Science Foundation of China

Disclosure: W. Sun, Z. Zhang: I identify that no financial interest in products or processes involved in their research.

The gene expression levels of gamma-glutamyl hydrolase in tumor tissues may be a useful biomarker for proper use of S-1 and tegafur-uracil/leucovorin in preoperative chemoradiotherapy in patients with rectal cancer


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Background: Preoperative chemoradiotherapy (CRT) with 5-FU-based chemotherapy is the standard of care for locally advanced rectal cancer. Both S-1 and tegafur-uracil/leucovorin (FT) are 5-FU-based oral drugs. S-1 is a mixture of tegafur, uracil and ooxoaliquin, whereas potassium metabolizes to levofoluforin (LV) to enhance the effect of 5-FU. S-1 is used without LV and causes the stronger antitumor effect than UFT/LV. We examined the association of the response to CRT with the gene expression levels of CRT-related genes in tumor tissues before CRT.

Methods: Data of 51 patients (pts) with locally advanced rectal cancer who received preoperative CRT at a total radiation dose of 45 Gy with S-1 or UFT/LV for 5 weeks were analyzed. The pathological tumor response was assessed according to the tumor regression grade (TRG) criteria. A patient with TRG 3-4 was defined as a responder. The expression levels of CRT-related 18 genes in tumor tissues were determined using a RT-PCR assay. The relationships between tumor response and the gene expression levels were analyzed. The cutoff value for gene expression of gamma-glutamyl hydrolase (GGH) was determined by the ROC curve.

Results: Pathological response (TRG 1-2) and pathological complete response (pCR) was observed in 23 pts (45.1%) and 8 pts (15.7%), respectively. The expression levels of methyltetrahydrofolate dehydrogenase and phosphoribosyl synthetase (GART) were significantly higher in the pCR pts than in the non-pCR pts (p = 0.0091 and p = 0.0477). In UFT/LV group, the gene expression levels of methyltetrahydrofolate reductase (MTHFR) and GGH were significantly lower in the responders than in non-responders (p = 0.0386 and p = 0.0579). The total pathological response rate of both high-GGH pts in S-1 group and low-GGH pts in UFT/LV group was 65.2%, and was higher than that (45.1%) in all pts.

Conclusions: The expression levels of genes related to folate metabolism in tumor tissue were associated with response to preoperative CRT including S-1 or UFT/LV. In particular, the gene expression level of GGH in tumor tissues may be a useful biomarker for determining which regimen, S-1 or UFT/LV, should be used in CRT.

Legal entity responsible for the study: N/A

Funding: Tokai University

Disclosure: H. Nagase: Is an employee of Taiho Pharmaceutical Co. Ltd. All other authors have declared no conflicts of interest.
paracortex, and the medulla, and consist mainly of T cells, B cells, natural killer (NK) cells, and histocytes. We studied the relations of the T-cell region, B-cell region, and the number of NK cells to the number of retrieved LNs, LN size, and outcomes.

Methods: The study group comprised 320 patients with stage II colon cancer who underwent curative resection from 1991 through 2003. All operations were performed by the same team and LN dissection was performed to the origin of the feeding artery. LN with maximum long axis diameter (maximum LN) was selected in each patient and immunostained with CD3 as a T-cell marker, CD20 as a B-cell marker, and CD56 as an NK-cell marker. CD3-positive area ratio and CD20-positive area ratio were calculated using the image analyzer. The number of CD56-positive cells was counted at six sites and the mean number per 0.093 mm² was calculated.

Results: The number of retrieved LNs was 14.8 ± 10.1 (mean ± SD). The mean CD3-positive area ratio was 0.39 ± 0.08. The mean CD20-positive area ratio was 0.42 ± 0.10. The mean number of CD56-positive cells was 10.7 ± 9.6. Multivariate analysis showed that the diameter of the maximum LN significantly correlated with the following variables (in the order of the strongest to weakest): number of CD56-positive cells, age, tumor location, CD20-positive area ratio, and sex. The number of retrieved LNs positively correlated with tumor location, age, number of CD56-positive cells, and CD20-positive area ratio. The median follow-up was 118 months. Multivariate analysis showed that age, tumor location, T stage, CD20-positive area ratio, and the number of CD56-positive cells were independent prognostic factors of survival.

Conclusions: B-cell area ratio and the number of NK cells in maximum LNs were independent prognostic factors related to LN size, the number of retrieved LNs and survival in Stage II colon cancer.

Legal entity responsible for the study: N/A

Funding: Tokai University

Disclosure: All authors have declared no conflicts of interest.

Association between HER2 amplification and cetuximab efficacy in patients with RAS wild-type metastatic colorectal cancer

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Background: Cetuximab has shown clinical benefit in patients with metastatic colorectal cancer (mCRC) harbouring wild-type RAS. HER2 amplification has been suggested as one of the resistant mechanisms of cetuximab treatment. We evaluated association between HER2 amplification and cetuximab efficacy in mCRC patients harbouring extended RAS wild-type.

Methods: Between December 2003 and June 2013, we found 253 mCRC patients whose tumor harboured wild type in exon 2/3/4/5 of both KRAS and NRAS by high throughput sequencing (OncoMap version 4.0) and were treated with cetuximab as ≥2nd or later-line. We finally included 243 mCRC cases whose HER2 status could be determined by both immunohistochemical (IHC) scoring according to HER2ACs criteria and silver in-situ hybridisation (SISH). Progression-free survival (PFS) and overall survival (OS) were analysed in homogenous group (n = 149) who were progressed after oxaliplatin, irinotecan and fluoropyrimidines.

Results: The median age was 55 years (range 19–76 years); 168 patients (69.1%) were male. Of the 243 RAS wild-type tumour, we observed 11 cases (4.5%) of HER2 amplification (10.1 vs 13.5 months, p = 0.408).

Table: S21P

<table>
<thead>
<tr>
<th>HER2 IHC (HER2ACs criteria)</th>
<th>SISH Negative</th>
<th>Equivocal</th>
<th>Positive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplification</td>
<td>11</td>
<td>9</td>
<td>11</td>
<td></td>
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<tr>
<td>No amplification</td>
<td>229</td>
<td>4</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>240</td>
<td>4</td>
<td>244</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: HER2 amplification is associated with shorter PFS after cetuximab in mCRC patients harbouring extended RAS wild-type. Recent study of dual targeting of EGFR and HER2 demonstrated promising result; further study is warranted for this population.

Legal entity responsible for the study: Asian Medical Center

Annals of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Broad detection of alterations predicted to confer lack of benefit from EGFR antibodies or sensitivity to targeted therapy in advanced colorectal cancer

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Background: Kras mutation represented the first genomic biomarker to predict lack of benefit from anti-EGFR antibody therapy in advanced colorectal cancer (CRC). Expanded RAS testing has further refined the treatment approach, but understanding of genomic alterations underlying primary and acquired resistance is limited.

Methods: We prospectively analyzed 4,422 clinical samples from patients with advanced CRC using hybrid-capture-based comprehensive genomic profiling (CGP) at the request of the individual treating physicians. Comparison with prior molecular testing results when available was performed to assess concordance.

Results: We identified RAS/RAF pathway mutation or amplification in 62% of cases, including samples harboring KRAS mutations outside of the codon 12/13 hotspot region in 6.4% of cases. Among cases with KRAS non-codon 12/13 alterations for which prior test results were available, 79/90 (88%) were missed by focused testing. Of 1,644 RAS/Raf wild-type cases analyzed by CGP, 28% harbored a genomic alteration (GA) associated with resistance to anti-EGFR therapy in advanced CRC including mutation of PIK3CA, EGFR, and ERBB2 genes. We also identified other targetable GA including novel kinase fusions, RTK amplification, activating point mutations, as well as microsatellite instability.

Conclusions: Comprehensive genomic profiling reliably detects alterations associated with lack of benefit to anti-EGFR therapy in advanced CRC while simultaneously identifying alterations potentially important in guiding treatment. The use of CGP during the course of clinical care allows for the refined selection of appropriate targeted therapies and clinical trials, increasing the chance of clinical benefit and avoiding therapeutic futility.

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Foundation Medicine, Inc.

Disclosure: S. J. Klemperer; Has received honoraria from Foundation Medicine. A. Rankin, R.L. Erlich, J. Sun, J.S. Ross, P.J. Stephens, V.A. Miller, S. Ali, A.B. Schrock; Employee and stock ownership in Foundation Medicine. All other authors have declared no conflicts of interest.

Mutational profiles in paired primary tumours and metastases in colorectal cancer patients: an NGS study of the Hellenic Cooperative Oncology Group

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Background: Clonal heterogeneity in cancer contributes to resistance to therapy. The comparison of the genetic profile of primary tumours with that of metastases will inform clinical decision-making for advanced colorectal cancer patients.

Methods: Formalin-fixed paraffin-embedded colorectal adenocarcinoma from primary tumours (CRCp) and metastases (CRCm) from 82 patients managed according to H-COG protocols were assessed. Next Generation Sequencing (Ion PROTON) was applied for mutational profiling of 51 cancer-related genes and 6 non-coding RNAs (444 amplicons, 48000 bases, median reading depth >1300x). 57 patients had synchronous and 25 metachronous metastases. Intervening lines of therapy between primary tumour to resection of metastases were administered in 46 patients.

Results: The most frequently mutated genes in CRCp were TP53 45%, KRAS 32%, APC 27%, IGFIR 8.5%, CDH1 8.5%, whereas in CRCm TP53 48%, APC 30%, KRAS 27%, IGFIR 9.8%, PIK3CA 9.8%. Concordance rates between paired CRCp and CRCm were high (77–96%) for the commonly mutated genes. A trend for increasing

Table: S21P

<table>
<thead>
<tr>
<th>HER2/CEP17 ratio 3.3</th>
<th>HER2/CEP17 ratio 2.7</th>
<th>HER2/CEP17 ratio &gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>

Conclusions: HER2 amplification is associated with shorter PFS after cetuximab in mCRC patients harbouring extended RAS wild-type. Recent study of dual targeting of EGFR and HER2 demonstrated promising result; further study is warranted for this population.

Legal entity responsible for the study: Asian Medical Center

Annals of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.
concordance of the mutational status was observed in metachronous as compared to synchronous metastases. Higher mutational discordance was observed when therapy intervened between CRCp and CRCm. We observed co-existence of mutational discordance in genes related to several functional groups, suggesting clonal divergence affecting the genome diffusely. We will present more data on mutated allele frequencies in shared as well as in private mutations in CRCp and CRCm and analyse the impact on patient outcome.

### Table: 523P %Mutational discordance CRCp vs CRCm by time and exposure to therapy

<table>
<thead>
<tr>
<th>GENE</th>
<th>Metachronous</th>
<th>Synchronous</th>
<th>Not exposed to tx</th>
<th>Exposed to tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>31</td>
<td>18</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>APC</td>
<td>24</td>
<td>12</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>KRAS</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>IGFR1</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>CDH1</td>
<td>10</td>
<td>8</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>HER4</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>SMAD2</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>BRAF</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>NRAS</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Conclusions: Although a high concordance rate for frequently mutated genes was seen in CRCp versus CRCm, a trend was observed for increasing discordance with metachronous appearance of metastases and with prior exposure to antineoplastic therapy.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group

Disclosure: All authors have declared no conflicts of interest.

### 524P Phase II study to evaluate the efficacy of regorafenib in metastatic colorectal cancer patients by the assessment using FDG-PET/CT (JACCRO CC-12) metastatic colorectal cancer (JACCRO CC-12)

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Background: Regorafenib (REG) have been approved as salvage treatment for patients targeting agents, as compared with the change of tumor burden using conventional CT. We conducted a prospective study to evaluate the efficacy of REG in mCRC patients by the assessment using FDG-PET/CT.

### Methods: Patients with mCRC refractory to standard chemotherapy with measurable lesions according to RECIST (Ver. 1.1) criteria, which are also assessable by FDG-PET/CT, enrolled in this study. REG was given orally in a dose of 160 mg once-daily for 3 weeks, followed by 1 week of rest. After the first cycle, FDG-PET/CT was performed again to assess the chronological change in the SUV max as compared with that before the treatment. The primary endpoint is the chronological change in SUV max in the lesion, of which value is highest in pretreatment FDG-PET/CT. Metabolic response and size-based response were assessed according to EORTC PET and RECIST criterion, respectively, by independent external review. We set the null and alternative hypotheses at 0% and 10%, respectively. Assuming a one-sided α level of 2.5% and power of 80%, we estimated that 16 subjects are required and set the target sample size at 20 patients.

### Results: From November 2014 to March 2016, 17 of all enrolled 20 patients were evaluated for metabolic response. Six and 11 patients had SD and PD for the best metabolic response, respectively. When response was categorized into PD and non-PD (PR or SD), the metabolic response after the first cycle could predict the size-based response with a sensitivity of 83% and specificity of 100%.

### Conclusions: We confirmed the efficacy of REG in mCRC patients by the assessment of metabolic response using FDG-PET/CT.

Clinical trial identification: UMIN000015563, Nov 01 2014

Legal entity responsible for the study: Masato Nakamura

Funding: Bayer

Disclosure: All authors have declared no conflicts of interest.

### 525P KRAS mutations in circulating tumour DNA (ctDNA) in MIR-defined, high-risk, locally-advanced rectal cancer (LARC) patients (pts) from the EXPERT-C trial


### Background: Although the potential of detecting ctDNA in solid tumours has been increasingly reported, there are limited data in LARC. We sought to investigate frequency and relevance of KRAS mutations in ctDNA in a randomised phase II trial of CAPOX followed by chemoradiotherapy, surgery and adjuvant CAPOX×ctezibux in high-risk LARC.

### Methods: RAS (exon 2-4) mutations were previously analysed in the biopsy and resection samples using standard sequencing techniques. ctDNA was isolated from 2 ml of plasma collected prior to treatment start and analysed by digital droplet PCR. Commerially available and validated assays were used to detect KRAS mutations (G12D, G12V or G13D in all pts plus any patient-specific, additional mutation previously detected in the tissue). The sensitivity cut-off for the assay of ctDNA was set at a lower limit of 0.02% mutant alleles.

### Results: 97/164 study pts (59%) were assessable for ctDNA. G12D, G12V or G13D tissue mutations were previously identified in 28 pts (7 not assessable): KRAS mutations in ctDNA in these codons were found in 13/28 (46%) and 22/62 (35%) of pts who were KRAS mutant and wild type in tissue, respectively: 5/10 pts with G12A, G12C or G13D tissue mutations had the same mutation in the blood. Among 38 pts with any KRAS tissue mutation, ctDNA was detected in 18 pts (47%) and associated with a higher baseline T stage (p = 0.01). However, no association was found with complete response (CR) (16.7% vs 10%, p = 0.63), PFS (HR 0.86, 95% CI: 0.31-2.37, p = 0.77) or OS (HR 0.92, 95% CI: 0.32-2.65, p = 0.88). When tissue and ctDNA mutation data were combined to redefine the mutation status of the assessable EXPERT-C study population (n = 119), the RAS wild type and 87 RAS mutant, no interaction was found between RAS status and cetuximab treatment with regards to CR (p = 0.99), PFS (p = 0.57) or OS (p = 0.98).

### Conclusions: In this series of high-risk LARC, KRAS mutations in ctDNA were found in up to one third of pts with KRAS mutant and KRAS wild-type tumours, respectively, as defined by previous tissue mutation analyses. Larger studies are needed to better address the potential role of ctDNA as a prognostic or predictive tool in LARC.

Clinical trial identification: ISRCTN registration: 99828560

Legal entity responsible for the study: The Royal Marsden NHS Foundation Trust and Institute of Cancer Research

Funding: The NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research

Disclosure: I. Chau: Advisory roles with Merck Serono, Roche, Sanofi Oncology, Bristol Myers Squibb, Eli-Lilly, Novartis, Gilead Science. Research funding from Merck-Serono, Novartis, Roche and Sanofi Oncology. Honoraria from Roche, Sanofi-Oncology, Eli-Lilly, Taiho. D. Cunningham: Research funding from: Roche, Amgen, Celgene, Sanofi, Merck Serono, Novartis, AstraZeneca, Bayer, Merrimack and MedImmune. A. Cervantes: Advisory roles with Merck-Serono and Roche. Research funding from Roche. Honoraria from Roche and Merck-Serono. All other authors have declared no conflicts of interest.
Tracking emerging KRAS and BRAF mutations through cfDNA in colorectal cancers treated with EGFR blockade

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Background: Oncogenic KRAS mutations can predict lack of response by colorectal cancer (CRC) to epidermal growth factor receptor (EGFR) blockade. Although KRAS status is usually determined through primary tumor biopsies, genomic profiles of their metastases may differ because of intrinsic molecular heterogeneity. We used circulating cell-free DNA (cfDNA) to genotype CRC, and then to track clonal evolution during treatment with EGFR blockade, to evaluate the utility of cfDNA to detect KRAS and BRAF mutations before and during chemotherapy.

Methods: We enrolled 55 patients with metastatic CRC, with no KRAS mutations in their primary tumors. Before starting chemotherapy, cfDNA was purified from 1 ml serum from each patient. We detected 9 KRAS (G12A, G12R, G12D, G12C, G12S, G12V, G13D, Q61H, and Q61R) and BRAF (V600E) mutations, using the Invader method and digital PCR. Of the 55 patients, 24 were treated with systemic chemotherapy that included EGFR blockade. We extracted cfDNA from these patients every 2–3 months until disease progression.

Results: KRAS mutations in cfDNA were detected in 5 patients before chemotherapy (9% [5/55], 12.3% patients, codon 13: 2 patients). The response rate was 83% (20/24), 3 of the 4 non-responders were patients whose KRAS mutations were detected by cfDNA before chemotherapy. The response rate of patients with no KRAS mutations in cfDNA before chemotherapy was 95% (20/21). Of these 20 initially responsive patients, 10 (50%) acquired resistance. In 5 of these 10 patients (50%) cfDNA detected emerging KRAS mutations. Three of these 5 patients had multiple mutations, including codon 12. Mutations in codon 61 were detected in 3 patients, but no solo codon-61 mutations were detected. BRAF mutations were also detected in 3 patients, but no solo BRAF mutations were detected.

Conclusions: EGFR blockade had no beneficial effect for patients in whom cfDNA detected KRAS mutations in their primary tumor. Emerging KRAS or BRAF mutations that were undetected before starting chemotherapy can lead to acquired resistance to EGFR blockade. However, emerging KRAS or BRAF mutations were detected in only

Table: S27P

<table>
<thead>
<tr>
<th></th>
<th>EGFR status</th>
<th>FOLFOX-4 + cetuximab (n = 173)</th>
<th>FOLFOX-4 + cetuximab vs FOLFOX-4 (HR [95% CI])</th>
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</thead>
<tbody>
<tr>
<td></td>
<td># of pts</td>
<td># of pts</td>
<td>PFS, median (mo)</td>
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<td></td>
<td></td>
<td>FOLFOX-4 (n = 181)</td>
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<td></td>
<td></td>
<td></td>
<td>ORR, % FOLFOX-4 + cetuximab vs FOLFOX-4 (HR [95% CI])</td>
</tr>
<tr>
<td>Percentage of positively-staining cells</td>
<td>0%</td>
<td>85</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>&gt; 5%-10%</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>&gt; 35%</td>
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<td>28</td>
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</table>

EGRF-expressing mCRC. In this prospective subgroup analysis of the randomized phase 3 TAILOR trial, we evaluate the impact of EGFR status on the efficacy of FOLFOX-4 + cetuximab in the first-line treatment of Chinese pts with RAS-wt mCRC.

Methods: TAILOR is a randomized phase 3 trial that includes a modified intention-to-treat (ITT) population of 393 Chinese pts with RAS-wt mCRC treated with FOLFOX-4 + a cetuximab. The primary endpoint of TAILOR is progression-free survival (PFS); secondary endpoints include overall survival (OS) and overall response rate (ORR). Tumor EGFR detectability was assessed in evaluable pts within the mITT population via immunohistochemistry.

Results: Within the mITT population, 193 pts with RAS-wt mCRC were randomized and treated with FOLFOX-4 + cetuximab and 200 pts received FOLFOX-4. Adding cetuximab to FOLFOX-4 significantly improved median PFS (9.2 vs 7.4 mo, HR [95% CI] = 0.691 [0.536-0.891]; p = .004), preliminary assessment of median OS (20.7 vs 17.8 mo, HR [95% CI] = 0.762 [0.607-0.958]; p = .020), and ORR (61.1% vs 39.5%, odds ratio = 2.410 [1.607-3.614]; p < .001). Among 354 EGFR-evaluable pts in the mITT population, efficacy gains in PFS and ORR were independent of tumor EGFR status (Table).

Conclusions: Irrespective of tumor EGFR status, the addition of cetuximab to first-line FOLFOX-4 clearly improved PFS and ORR in Chinese pts with RAS-wt mCRC. The TAILOR study data confirm cetuximab in combination with chemotherapy as a standard-of-care first-line treatment regimen for pts with RAS-wt mCRC, independent of tumor EGFR status.

Clinical trial identification: EMR62202-057, NCT01228734

Legal entity responsible for the study: N/A

Funding: Merck KGaA, Darmstadt, Germany

Disclosure: J. Chen, J. Liu. Employee of Merck Serono Co., Ltd., Beijing, China. S.P. Eggleton. Employee of Merck KGaA, Darmstadt, Germany. J. Li. Research Funding from Merck and Roche. All other authors have declared no conflicts of interest.

Abstracts

tracking emerging KRAS and BRAF mutations through cfDNA in colorectal cancers treated with EGFR blockade

S27P

Impact of tumor epithelial growth factor receptor (EGFR) status on the outcomes of first-line FOLFOX-4 + cetuximab in patients (pts) with RAS-wild-type (wt) metastatic colorectal cancer (mCRC) in the randomized phase 3 TAILOR trial

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Background: Cetuximab in combination with chemotherapy (either FOLFIRI or FOLFOX) is a standard-of-care first-line treatment for pts with RAS-wt,
Factors associated with discordance of KRAS, NRAS, BRAF, PIK3CA mutation status in the primary tumor and metastases in patients (pts) with colorectal cancer (CRC)

V. Taly2, P. Laurent-Puig4

All authors have declared no conflicts of interest.

Background: The concordance of KRAS gene mutation status between the primary and metastatic CRC is 99%. The aim of this study was to find factors associated with the discordance of KRAS, NRAS, BRAF, PIK3CA mutation status between the primary tumors and metastases in pts with CRC.

Methods: We performed DNA melting analysis with TaqMan probes and followinganger sequencing to detect mutation hot-spots in KRAS exons 2 and 3, NRAS exons 2 and 3, BRAF exon 15, PIK3CA exons 9 and 20 in 148 tumor tissues from 65 pts (65 primary tumors and 83 metastases). Average age of all pts was 57 years (31-76), of male pts - 48%. The average number of metastases in one pt was 1.3 (1-5). Primary tumors were located in the right, left part of colon and rectum in 10.8%, 35.4% and 53.8% respectively. The median time between the resection of the primary tumor and metastasectomy was 13 mon. (1-63). Most pts (88%) received chemotherapy before metastasectomy. None of the pts received anti-EGFR Mabs. Statistical analysis was performed using SPSS v.22, Inc, Chicago, IL.

Results: Mutations in KRAS, NRAS, PIK3CA and BRAF genes in primary tumors were detected in 43.1%, 3.1%, 13.8% and 3.1%, respectively. Discordance of mutation status of genes was identified in 29.2% of pts: 16.9% in KRAS, 3% in NRAS, 12.3% in PIK3CA and 3% in BRAF status. In all cases of metastases 10.8% detected in 43.1%, 3.1%, 13.8% and 3.1%, respectively. Discordance of mutation status (p = 0.08). Also, peritoneal metastasis did not influence the discordance in mutation status.

Conclusions: We detected clinical significant differences in KRAS, NRAS, PIK3CA and 3% BRAF status. In all cases of metastases in the brain we found the concordance of KRAS gene mutation status between the primary tumor and metastasectomy was 13% (1-63). Most pts (88%) received chemotherapy before metastasectomy. None of the pts received anti-EGFR Mabs. Statistical analysis was performed using SPSS v.22, Inc, Chicago, IL.

Prognostic value of circulating tumor DNA in advanced colorectal cancer patients: Quantification of hypermethylated or mutant sequences using picoliter droplet digital PC


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Background: The identification of patient (pt) characteristics associated with dermatologic toxicity severity during treatment with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies could inform treatment choices for patients with metastatic colorectal cancer.

Methods: Data from the randomized, first-line, phase 3 PRIME trial of panitumumab (Pmab) and chemotherapy arms from 20050181 and PRIME, pts with grade 2–4 dermatologic toxicity severity with pt characteristics/laboratory values and treatment results. This study was supported by Amgen Inc.

Results: In the pmab arms from 20050181 and PRIME, pts with grade 2–4 dermatologic toxicity consistently had a trend of lower neutrophil-to-lymphocyte ratio (NLR) vs those with grade 0–1 (Table). In the pmab + FOLFIRI group when each was compared with grade 0–1 dermatologic toxicity pts (Table). Among pts with progression-free survival ≥2 days, those with grade 2–4 dermatologic toxicity had improved overall survival and progression-free survival compared with pts with grade 0–1 toxicity (Table).

Conclusions: This study did not clearly identify pt characteristics that are potential dermatologic toxicity biomarkers; further studies are required to understand the relationship between NLR and dermatologic toxicity severity. Increased dermatologic toxicity severity was associated with improved clinical outcomes.

Prognostic value of circulating tumor DNA (ctDNA) in metastatic colorectal cancer (mCRC) needs to be validated in prospective clinical studies using precise and robust procedures. In this context, picoliter droplet digital PC has arisen as a highly sensitive and quantitative approach offering a broad dynamic range of detection. Methods: All consecutive mCRC patients receiving chemotherapy were included in this monocentric prospective study between October 2012 and April 2015. Plasma samples were collected before the first cycle of chemotherapy, then at 14 and 28 days. For each patient, tumor DNA from biopsies was tested for the presence of KRAS, BRAF and TP53 mutations either by conventional qPCR or Next-Generation Sequencing. When no mutation was identified in the tumor, ctDNA was screened for hypermethylated sequences of WIFI and NPY genes. CtDNA sequences (mutated or hypermethylated) were quantified (concentration, ng/mL) using picoliter droplet digital PC coupled to Taqman probes. Impact of ctDNA on survival and tumor response (RECIST 1.1) was analyzed using the Cox model with adjustment on age, sex and Kohn score.

Results: Overall, 113 patients were included. Preliminary results are focused on 70 mCRC patients treated with first-line chemotherapy (mean age: 65.7 yr [35.1–90.7]; male, 58.6%). The concentration of baseline ctDNA was significantly associated with a worse overall survival (OS) (first vs third tertile: H= 17.9; CI95% [1.9–22.2]; p = 0.046). At 14 or 28 days, patients with ctDNA concentrations remain above 0.2ng/mL have a significantly worse progression free survival (PFS) (HR 7.1, CI95% [2.3–21.9]; p = 0.001). Reduction in ctDNA level at 14 or 28 days under 0.2 ng/mL was significantly associated with CT tumor responses at 8 weeks (p = 0.05).

Conclusions: This study suggests that ctDNA is a significant prognostic factor in mCRC able to predict PFS and tumor response precociously. The quantifying circulating tumor DNA by picoliter droplet digital PCR in mCRC appears to be relevant to tailor the treatment of mCRC.

References:

Results:
A predictive model for 5-year disease-free survival (DFS) and overall survival (OS) was constructed using Kaplan-Meier analysis, logistic and Cox regression.

Efficacy Outcomes, n
Overall survival (months), median (95% CI)
10.7 (7.8–14.5) 9.1 (7.4–10.9)
Progression-free survival (months), median (95% CI)
3.9 (3.5–8.6) 4.5 (3.9–5.8)

Hazard ratio (95% CI)
0.51 (0.35–0.74) 0.75 (0.59–0.96)

Conclusions: MiRNA-192-3p is a promising biomarker for stage III B colon cancer patients. MiRNA-192-3p had no predictive value in this setting.

Legal entity responsible for the study: P. Li, Q. Ou, G. Chen, F.S. Oduncu

Funding: Sun Yat-sen University

Disclosure: All authors declare no conflicts of interest.
Conclusions: The overall agreement between plasma and tissue RAS mutation status indicates that blood-based testing with OncoBEAM™ RAS CRC is a viable alternative to tissue testing for mCRC patients. Moreover, this study shows that BEAMing will be useful to monitor RAS mutation status in patients undergoing systemic therapy to monitor resistance and evaluate the efficacy of particular treatments.

Legal entity responsible for the study: Cancer Program, IMIM-Hospital del Mar, Barcelona, Spain

Funding: Cancer Program, IMIM-Hospital del Mar, Barcelona, Spain Liquid Biopsy Analysis Unit, Health Research Institute of Santiago (IDIS). Complejo Hospitalario Universitario de Santiago de Compostela, Spain

Disclosure: All authors have declared no conflicts of interest.

<table>
<thead>
<tr>
<th>Table: 535P</th>
<th>Characteristics and demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≤ 30</td>
<td>BMI &gt; 30</td>
</tr>
<tr>
<td>a (%)</td>
<td>474 (84%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 12</td>
</tr>
<tr>
<td>ECOG ≤ 1</td>
<td>402 (85%)</td>
</tr>
<tr>
<td>Female</td>
<td>170 (57%)</td>
</tr>
<tr>
<td>Metastases</td>
<td>215 (46%)</td>
</tr>
<tr>
<td>Liver</td>
<td>147 (31%)</td>
</tr>
<tr>
<td>Multiple The</td>
<td></td>
</tr>
<tr>
<td>other sites</td>
<td></td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
</tr>
<tr>
<td>Hi + BEV</td>
<td>308 (65%)</td>
</tr>
<tr>
<td>IO + BEV</td>
<td>142 (30%)</td>
</tr>
<tr>
<td>F + BEV</td>
<td>24 (5%)</td>
</tr>
<tr>
<td>KRAS status</td>
<td></td>
</tr>
<tr>
<td>Wild</td>
<td>157 (85%)</td>
</tr>
<tr>
<td>Mутant</td>
<td>18 (5%)</td>
</tr>
</tbody>
</table>

Conclusions: Efficacy of bevacizumab may be lower in obese patients. Prospectively designed studies for obese patients should be done to recommend the efficacy of bevacizumab in mCRC.

Legal entity responsible for the study: N/A

Funding: Turkish Oncology Group (TOG)

Disclosure: All authors have declared no conflicts of interest.

Table: 535P Concordance of KRAS, NRAS and BRAF status between primary colorectal tumors and paired metastasis (mts)

<table>
<thead>
<tr>
<th>MTS</th>
<th>Pt-Liver mts</th>
<th>Pt-Extrahepatic mts</th>
<th>Pt-Any location mts</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>78.9% (15/19)</td>
<td>72.7% (8/11)</td>
<td>76.7% (95% CI 59.9-93.5)</td>
</tr>
<tr>
<td>NRAS</td>
<td>66.7% (4/6)</td>
<td>71.4% (5/7)</td>
<td>71.4% (95% CI 29.0-96.3)</td>
</tr>
<tr>
<td>BRAF</td>
<td>100% (5/5)</td>
<td>100% (1/1)</td>
<td>100% (95% CI 54.1-100)</td>
</tr>
</tbody>
</table>

We found that discordant pairs of pt-liver mts for KRAS showed more frequently a percentage of tumor cells in pt samples <70% (60% of cases versus 40% for concordant cases; p = 0.044). Moreover, a trend for higher concordance of KRAS was shown for colon compared to rectal primaries (86.7% versus 50%, p = 0.178).

Conclusions: Concordance rate of approximately 80% can be found between pt and corresponding mts in unselected population of CRC patients. Concordance of tumor cells in samples can affect results. More studies are needed to clarify causes for discordance in mutational status of different samples from the same patient.

Legal entity responsible for the study: Hospital Costa del Sol

Funding: Hospital Costa del Sol

Disclosure: All authors have declared no conflicts of interest.
low SII and NLR sufficient lymph node sampling (more than 12 lymph nodes dissection) may prevent unnecessary adjuvant chemotherapy in low risk patients. Their clinical utility should be validated in further studies.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**E17P**

Circulating microRNA-126 and epidermal growth factor-like domain 7 protein predict recurrence of colon cancer in patients treated with neoadjuvant chemotherapy

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Background: Neoadjuvant chemotherapy represents a new treatment approach for patients with locally advanced colon cancer. The aim of this study was to analyze the prognostic impact of circulating microRNA-126 (miRNA-126) and epidermal growth factor-like domain 7 (EGF7) in patients with locally advanced colon cancer treated with neoadjuvant chemotherapy.

Methods: All 71 patients from a phase II trial were included. Sampling of peripheral blood was carried out before initiation of neoadjuvant chemotherapy, before operation, and at the first post-operative control. The diagnostic biopsy and the resected tumour were sampled for tissue analyses. Circulating (cir-) EGF7 was analysed by serum by enzyme-linked immunoassay (ELISA) while cir-miRNA-126 was analysed by real-time qPCR by plasma samples. The tissue expression of miRNA-126 was assessed using in situ hybridization and immunoguided analyses.

Results: After a median follow-up of 4.0 years, disease had recurred in 14 patients. The 5-year disease free survival (DFS) and overall survival (OS) rates were 80% and 85%, respectively. Overall, cir-miRNA-126 and cir-EGF7 decreased during neoadjuvant chemotherapy. Patients with disease recurrence were characterized by a significantly lower miRNA-126 expression in the diagnostic biopsy (p = 0.049), and significantly lower levels of cir-miRNA-126 at baseline (p = 0.02), operation (p = 0.042), and control (p = 0.001), compared to patients without disease recurrence. High levels of cir-EGF7, assessed before operation, were associated with a higher recurrence rate (p = 0.019). These differences translated into significant differences in DFS and OS as well. A 5-year OS rate of 96% was demonstrated for patients with cir-miRNA-126 levels above the median.

Conclusions: Low levels of miRNA-126 and high levels of EGF7 seem to correlate with disease recurrence in patients with locally advanced colon cancer treated with neoadjuvant chemotherapy. These results are in accordance with previous studies in the adjuvant and metastatic setting collectively arguing for a clinical importance of these prognostic factors.

Clinical trial identification: ClinicalTrials.gov Identifier: NCT01108107

Legal entity responsible for the study: Department of Oncology, Vejle Hospital

Funding: Department of Oncology, Vejle Hospital

Disclosure: All authors have declared no conflicts of interest.

**E18P**

The genomic complexity of metastatic colorectal tumors by age, gender, race, and location of primary tumor using next-generation sequencing

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Background: Recent molecular profiling has identified a growing number of mutations that are considered targetable in metastatic colorectal cancer (mCRC). We aimed to explore the genomic complexity of metastatic colorectal tumors by patient factors such as age, gender, race, and site of primary tumor using next-generation sequencing (NGS).

Methods: We conducted a retrospective study based on comprehensive genomic profiling of tumors from patients (pts) with predominantly mCRC at our single institution using NGS via FoundationOne. All classes of genomic alterations were identified and their frequencies analyzed according to age (<50 and ≥ 60 years old), gender, race, and location of primary tumor.

Results: Among 210 tumors that underwent FoundationOne analysis, frequencies of the following mutations in pts <50 were significantly different than in pts ≥ 60: APC (75.8% vs. 39.9%, Fisher’s exact test-2 sided p = 0.0384), ARID (3.0% vs. 16.3%, p = 0.0088), KRAS (9% vs. 5.5%, p = 0.0453), and FLT (9% vs. 0.8%, p = 0.019). The following mutations in females (n = 92) significantly differed in frequency than in males (n = 118): ACVR1B (4.3% vs. 0%, p = 0.035), ARID (7.3% vs. 11.9%, p = 0.0386), and FLT (9% vs. 0.8%, p = 0.0431). Mutational frequencies in metastatic colorectal tumors of the following were significantly different based on right colon (including transverse colon, n = 58) or left colon (including rectum, n = 120): BRAF (20.7% vs. 2.5%, p = 0.0011), DNM3TA (6.9% vs. 0%, p = 0.0105), FAM (15.5% vs. 2.5%, p = 0.0032), FAK (6.2% vs. 0%, p = 0.0334), FLT (12.1% vs. 3.3%, p = 0.0409), PIK3CA (45.4% vs. 12.5%, p = 0.0011), and PTEN (17.2% vs. 5.0%, p = 0.0113). BRCA mutations were the only ones that significantly differed in frequency based on race.

Conclusions: There is increased genomic complexity observed in several molecular alterations of potential significance in mCRC based on age, gender, race, and site of primary tumor. These findings inform ongoing studies of larger size and prospective design that aim to analyze molecular signatures in metastatic colorectal tumors and their significance to prognosis and therapeutic targeting.

Legal entity responsible for the study: City of Hope

Funding: City of Hope

Disclosure: All authors have declared no conflicts of interest.

**E19P**

Circulating pro-angiogenic markers in patients receiving first-line FOLFIRI + bevacizumab for metastatic colorectal cancer: angiogenesis-cENTRAL pre-planned analysis of the Italian Research Group for Digestive Tract Cancer (GISCAD)

CENTRAL trial (ColorEctalavrastINtRAlId)


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Background: CENTRAL was a phase II trial of first-line FOLFIRI + bevacizumab in patients with advanced colorectal cancer prospectively stratified according to serum LDH. A pre-planned exploratory analysis (Serum angiogenesis-cENTRAL) was conducted to identify changes in the concentrations of circulating pro-angiogenic factors during treatment as a potential predictive factor for efficacy/resistance.

Methods: Patients treated with first-line FOLFIRI + bevacizumab were prospectively assessed for the following circulating pro-angiogenic factors: hepatocyte growth factor (HGF), stromal derived factor-1 (SDF-1), placental derived growth factor (PLGF), fibroblast growth factor 2 (FGF2), macrophage chemotactic protein 3 ( MCP3), interleukin-8 (IL-8). Assessment was performed before start of treatment and at each cycle until treatment discontinuation. Evaluation was performed by an ELISA-based technique.

Results: 73 patients were evaluable for the SENTRAL analysis: in this population mPFS was 12.8 months and mOS was 24.5 months. Among tested circulating factors, FGF-2 levels correlated with clinical outcome in this population. In particular we observed progressive disease in respectively 1/35 (3%) patients showing an increase in FGF-2 levels starting from first cycle to first-radiological evaluation and in 8/38 (21%) patients showing a decrease in FGF-2 levels (p = 0.03). Median PFS for patients showing an increase in FGF-2 levels was 16.6 months vs 8 months for patients showing a decrease in FGF-2 levels (HR=0.68, 95%CI=0.37-1.13, p = 0.12). Improved overall survival for patients showing an increase in FGF-2 levels, compared to patients demonstrating a decrease in FGF-2 levels (24.8 vs 20.7 months, HR=0.43, 95%CI=0.19-0.98, p = 0.04) was also seen.

Conclusions: This preplanned, prospective analysis suggests that early increase (at 8-10 weeks timepoint) in circulating FGF-2 levels could be used as a marker to identify patients who are more likely to gain benefit from first-line FOLFIRI + bevacizumab based therapy.

Clinical trial identification: Trial protocol: EudraCT number 2012-005048-46

Legal entity responsible for the study: Gruppo Italiano per lo Studio dei Carcinomi del tratto Digerente (GISCAD)

Funding: GISCAD

Disclosure: All authors have declared no conflicts of interest.
Prospective evaluation of BRAF, PI3K and PTEN as predictive and prognostic biomarkers in first-line advanced KRAS wild-type colorectal cancer treated with FOLFIRI or FOLFI RI plus bi-weekly cetuximab. GEMCAD 10-02

Methods: We conducted a biomarker-evaluation phase II trial (ClinicalTrials.gov id: NCT01276379). We included 221 KRAS exon 2 WT patients and evaluated whole exome sequencing data and pathological response data. The DNA samples were sequenced for single nucleotide polymorphisms (SNPs) of biomarkers, including RAS (KRAS exons 3 and 4; NRAS exons 2, 3 and 4) and other 108 genes, using Ion Torrent Personal Genome Machine (PGM) sequencing. A 5% cutoff value was used to determine mutations.

Results: In primary group, interaction tests between biomarker status and treatment effect were performed for objective response rate, progression-free survival and overall survival. Nine potential predictive biomarkers were identified, including GNAS, GNAT3, NOTCH1, RBMXL3, ERBB2, MDN1, PTCH1 and LY6G6D. With RAS wild-type patients in primary group, we built a predictive model for the objective response to cetuximab plus chemotherapy with Logistic regression, employing 9 identified biomarkers (wild-type vs. mutant) and treatment (cetuximab plus chemotherapy vs. chemotherapy) as variables. Our predictive model classified patients in primary group very well (AUC = 0.81, 95% CI 0.72-0.90, P < 0.001). According to Youden index, 0.3666 was defined as cutoff value. Patients with predictive value higher than 0.3666 had better ORR (P = 0.001), DFS (P = 0.001) and OS (P = 0.009) than that with predictive value lower than 0.3666. For RAS wild-type patients in validation group, the predictive model also performed well (AUC = 0.79, 95% CI 0.71-0.87, P < 0.001). Patients with predictive value higher than 0.3666 also achieved better ORR (P = 0.04), DFS (P < 0.001). Thus, according to our model, patients with predictive value higher than 0.3666 were recommend to receive cetuximab plus chemotherapy.

Conclusions: Apart from RAS mutations, several new biomarkers were firstly correlated with efficacy of cetuximab, and our predictive model including these biomarkers was useful to further tailor the administration of cetuximab, but need further validation.

Clinical trial identification: N/A

Legal entity responsible for the study: Zhongshan Hospital, Fudan University

Funding: Merck KGaA

Disclosure: All authors have declared no conflicts of interest.

MicroRNA-31 overexpression is able to predict pathological response and outcome in locally advanced rectal cancer

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Background: The treatment of choice for locally advanced rectal cancer is preoperative chemoradiotherapy (CRT). Despite around half of patients do not respond, suffer unnecessary toxicities and surgery delays, there are no biomarkers to guide preoperative CRT outcome. MicroRNA-31 (miR-31) has been related to acquisition of 5-fluorouracil resistance in rectal cancer however its potential predictive value of response to preoperative CRT in locally advanced rectal cancer remains unknown.

Methods: Eight-two patients diagnosed with locally advanced rectal cancer who were preoperatively treated with 5-fluorouracil based CRT were selected for this study. The miR-31 expression was quantified in formalin-fixed paraffin-embedded biopsies from this cohort previous to CRT therapy administration and the results obtained were correlated with clinical and molecular characteristics, pathological response and outcome.

Results: Overexpression of miR-31 was found in 34.2% of the cases. Its overexpression significantly predicted poor pathological response (p = 0.018) and worse overall survival (OS) (p = 0.008). Multivariate analysis confirmed the clinical significance of miR-31 in determining pathological response to neoadjuvant CRT as well as OS.

Conclusions: miR-31 quantification emerges as a novel valuable clinical tool to predict both pathological response and outcome in locally advanced rectal cancer patients.

Legal entity responsible for the study: None

Funding: Fundacion Jimenez Diaz

Disclosure: All authors have declared no conflicts of interest.

Organ preservation using contact radiotherapy for early rectal cancer: outcomes of patients treated at a single centre in the United Kingdom

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Background: Contact radiotherapy for early rectal cancer utilizes 50kV x-rays to treat rectal cancers under direct vision as described by Papillon (1). We present data of a series of patients treated in a modern era at our centre in Hull, England, UK with prospective follow up.

Effects of beyond KRAS mutations on the efficacy of cetuximab plus chemotherapy for patients with unresectable colorectal liver-limited metastases (BELIEF: a retrospective biomarker analysis from a Chinese trial

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1Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, China, 2Department of Oncological Surgery, 1st Affiliated Hospital of Wenzhou Medical College, Wenzhou, China

Background: To identify predictive biomarkers for the efficacy of cetuximab.

Methods: 247 patients were recruited, including ITT patients of previous RCT (NCT01564810) (primary group) and a following cohort with same inclusion criteria of previous RCT (validation group). The DNA samples were sequenced for single nucleotide polymorphisms (SNPs) of biomarkers including the well-known “new” RAS (KRAS exons 3 and 4; NRAS exons 2, 3 and 4) and other 108 genes, using Ion Torrent Personal Genome Machine (PGM) sequencing. A 5% cutoff value was used to determine mutations.

Results: In primary group, interaction tests between biomarker status and treatment effect were performed for objective response rate, progression-free survival and overall survival. Nine potential predictive biomarkers were identified, including GNAS, GNAT3, NOTCH1, RBMXL3, ERBB2, MDN1, PTCH1 and LY6G6D. With RAS wild-type patients in primary group, we built a predictive model for the objective response to cetuximab plus chemotherapy with Logistic regression, employing 9 identified biomarkers (wild-type vs. mutant) and treatment (cetuximab plus chemotherapy vs. chemotherapy) as variables. Our predictive model classified patients in primary group very well (AUC = 0.81, 95% CI 0.72-0.90, P < 0.001). According to Youden index, 0.3666 was defined as cutoff value. Patients with predictive value higher than 0.3666 had better ORR (P = 0.001), DFS (P = 0.001) and OS (P = 0.009) than that with predictive value lower than 0.3666. For RAS wild-type patients in validation group, the predictive model also performed well (AUC = 0.79, 95% CI 0.71-0.87, P < 0.001). Patients with predictive value higher than 0.3666 also achieved better ORR (P = 0.04), DFS (P < 0.001). Thus, according to our model, patients with predictive value higher than 0.3666 were recommend to receive cetuximab plus chemotherapy.

Conclusions: Apart from RAS mutations, several new biomarkers were firstly correlated with efficacy of cetuximab, and our predictive model including these biomarkers were useful to further tailor the administration of cetuximab, but need further validation.

Clinical trial identification: N/A

Legal entity responsible for the study: Zhongshan Hospital, Fudan University

Funding: Merck KGaA

Disclosure: All authors have declared no conflicts of interest.

MicroRNA-31 overexpression is able to predict pathological response and outcome in locally advanced rectal cancer

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Background: The treatment of choice for locally advanced rectal cancer is preoperative chemoradiotherapy (CRT). Despite around half of patients do not respond, suffer unnecessary toxicities and surgery delays, there are no biomarkers to guide preoperative CRT outcome. MicroRNA-31 (miR-31) has been related to acquisition of 5-fluorouracil resistance in rectal cancer however its potential predictive value of response to preoperative CRT in locally advanced rectal cancer remains unknown.

Methods: Eight-two patients diagnosed with locally advanced rectal cancer who were preoperatively treated with 5-fluorouracil based CRT were selected for this study. The miR-31 expression was quantified in formalin-fixed paraffin-embedded biopsies from this cohort previous to CRT therapy administration and the results obtained were correlated with clinical and molecular characteristics, pathological response and outcome.

Results: Overexpression of miR-31 was found in 34.2% of the cases. Its overexpression significantly predicted poor pathological response (p = 0.018) and worse overall survival (OS) (p = 0.008). Multivariate analysis confirmed the clinical significance of miR-31 in determining pathological response to neoadjuvant CRT as well as OS.

Conclusions: miR-31 quantification emerges as a novel valuable clinical tool to predict both pathological response and outcome in locally advanced rectal cancer patients.

Legal entity responsible for the study: None

Funding: Fundacion Jimenez Diaz

Disclosure: All authors have declared no conflicts of interest.

Organ preservation using contact radiotherapy for early rectal cancer: outcomes of patients treated at a single centre in the United Kingdom

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Background: Contact radiotherapy for early rectal cancer utilizes 50kV x-rays to treat rectal cancers under direct vision as described by Papillon (1). We present data of a series of patients treated in a modern era at our centre in Hull, England, UK with prospective follow up.
Background: The selection of elderly patients with colorectal cancer (CRC) for adjuvant therapy remains a challenge. The main critical issue is to estimate if the patient risk of dying from non-cancer-related (NCR) causes predates cancer events. The aim of this paper is to evaluate whether an abbreviated Comprehensive Geriatric Assessment (aCGA) could predict survival and cancer mortality in high-risk resected CRC elderly patients candidates to adjuvant therapy.

Methods: 195 consecutive patients aged ≥75 with high-risk stage II and III CRC were prospectively enrolled. All patients underwent aCGA, which included comorbidity, polypharmacy, functional status, geriatric syndromes, mood, cognition and social support. According to aCGA results, patients were classified as “fit” (F), “medium fit” (MF) and “unfit” (UF) to receive standard therapy, adjusted treatment and best support care, respectively. Patients were followed up for at least 6 months or until death, and toxicity, survival and the cause of death were recorded. A competing risk approach was used to evaluate causes of death by oncogeriatric classification.

Results: 85 (44%) patients were classified as F, 56 (29%) as MF and 54 (27%) as UF. The 5-year survival rate was 74%, 52% and 27% in the F, MF and UF, respectively. At the end of the follow-up, 61 (31%) patients had died (14 F, 16 MF and 31 UF). The causes of death were cancer progression (CP), NCR, and unknown reason, in 54%, 46%, and 1%, respectively. There were no toxicities-related deaths. Overall population was more likely to die of CP rather than of NCR cause. However, stratifying by oncogeriatric categories, at the end of 5 years following surgery, 42% F, 32% MF and 15% UF patients died because of CP while <3% F or MF and 28% UF patients died because of NCR cause. In Fine and Gray adjusted model, UF patients were at significantly greater risk to die of NCR cause (sHR, 22.29 [CI95% 5.24 to 94.78]) and at significantly lower risk of dying of CP (sHR 0.30 [CI95% 0.09 to 0.96]) in comparison to F patients.

Conclusions: aCGA showed efficacy in predicting survival and competing risk of death in elderly patients with high-risk stage II and III CRC who underwent curative resection. aCGA is useful to shape adjuvant decision-making.

Legal entity responsible for the study: Institut Català d’Oncologia-Hospital Duran i Reynals

Funding: Institut Català d’Oncologia-Hospital Duran i Reynals

Disclosure: All authors have declared no conflicts of interest.
were used. Additionally, a subgroup analysis excluding patients with EOCG ≥ 2 at baseline was performed.

**Results:** Median TD (95% CI) was 5.5m (5.1-6.2) in the total safety population. In univariate analysis, EOCG > 1, which was only 14.6% of patients, and MNA were the only baseline parameters significantly associated with TD (p = 0.0006 and p = 0.0062, respectively), while G8 showed a trend (p = 0.0607). Significant correlations were observed for PFS vs. EOCG (p < 0.0001), MNA (p = 0.0001) and G8 (p = 0.0208) and for seven toxicity vs. EOCG (p < 0.0001) and G8 (p = 0.0105). When lowering the G8 cut-off to 12 (i.e. median value), both TD and PFS were significantly associated with G8 (p = 0.0093 and p = 0.0002, respectively). No significant correlation was observed for FRST. Multivariate analyses show significant correlations for EOCG vs. TD and PFS (p = 0.0047 and p < 0.0001, respectively) and for MNA versus PFS (p = 0.0007). The EOCG was no longer significant when excluding EOCG ≥ 2 patients.

**Conclusions:** In older mCRC patients, EOCG is a strong predictive marker for treatment duration and PFS, mainly driven by patients with EOCG ≥ 2. In the large group of patients with EOCG ≤ 1, MNA is a predictive marker for PFS.

**Clinical trial identification:** NCT01676922

**Legal entity responsible for the study:** Roche NV/SA Belgium

**Funding:** Roche NV/SA Belgium

**Disclosure:** All authors have declared no conflicts of interest.

**Table: 548P**

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<th>Age subgroups</th>
<th>ITT Population</th>
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<td></td>
<td>ORR PFS (95%CI)</td>
<td>Safety G3-4 diarrhea</td>
<td>G3-4 fatigue</td>
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<tr>
<td>&lt; 65</td>
<td>57.5% 8.9 (7.2-10.7) 23% 28%</td>
<td>58.3% 9.5 (6.9-12.1) 56.4% 11.2 (8.0-14.4)</td>
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<tr>
<td>≥ 65</td>
<td>52.6% 9.6 (8.4-10.9) 35% 33%</td>
<td>51.2% 10.5 (8.5-12.5) 57.1% 12.3 (5.7-18.9)</td>
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<tr>
<td>≥ 70</td>
<td>58.3% 9.6 (8.3-11.0) 24% 31%</td>
<td>58.8% 9.5 (7.6-11.4) 57% 11.2 (8.2-14.3)</td>
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<tr>
<td>≥ 75</td>
<td>51.2% 9.5 (6.9-12.0) 43% 26%</td>
<td>52.2% 12.0 (8.8-15.1) 52.9% 12.3 (5.7-18.9)</td>
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<tr>
<td>≥ 75</td>
<td>56.4% 9.4 (8.3-10.5) 25%* 31%*</td>
<td>68.0% 9.7 (8.1-11.3) 63.2% 11.0 (9.1-12.9)</td>
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<tr>
<td>≥ 75</td>
<td>57.1% 11.9 (10.0-13.9) 55%*</td>
<td>55.2% 13.1 (10.9-13.3) 77.8% 15.2 (11.7-18.7)</td>
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* p value < 0.05

**548P Clinical activity of FOLFI RI plus cetuximab in elderly patients (pts) according to extended gene mutation status by next generation sequencing (NGS) in the CAPRI- GOIM trial**

E. Martinei1, C. Carbone1, T. Troiani1, N. Normanno2, S. Picconi3, R. Bordonaro4, G. Francesco5, M. Biglietto6, C. Barone7, A.M. Rachiglio8, V. Montesarchio9, G. Tonin10, S. Cinieri11, D. Rizzi12, A. Febraro13, T.P. Latino14, G. Modoni15, G. Guiseppe6, E. Maiello6, F. Gardiello6

**Background:** Regorafenib (REG) is an oral multikinase inhibitor with survival benefit in salvage line therapy for metastatic colorectal cancer (mCRC), fatigue and malaise which are common adverse events (AEs) cause REG treatment discontinuation. Oral steroids are empirically used for treatment of cancer related fatigue, although there is no evidence of a predictive marker. This study aimed to evaluate the anti-fatigue effect of oral steroids through a double-blind placebo-controlled phase II study of prophylactic dexamethasone (DEX) therapy for fatigue and malaise due to regorafenib in patient (pts) with metastatic colorectal cancer (mCRC) [KSCC1402/HGSG1402].

**Methods:** Eligibility included mCRC, objective failure of standard therapy, ECOG performance status 0 or 1. ≥ Grade 1 fatigue or malaise was allowed to be enrolled in this study. Pts were 1:1 randomly assigned to an oral steroids group (dex 2 mg/day, 4 weeks) or a placebo (PLC) group with REG (160 mg/day, 3 weeks on/1 week off). The protocol period was scheduled for first 28 days of REG treatment. The primary endpoint was incidence of fatigue or malaise (CTCAE ver. 4, all grades) during the protocol period. Secondary endpoints included patient-reported outcome (PRO) (CTCAE and the Brief Fatigue Inventory, AIS), relative dose intensity of REG. Response, progression free survival and overall survival were also evaluated as exploratory endpoints.

**Results:** Between October 2014 and December 2015, 74 pts were enrolled and randomized (dex: 37, PLC: 37). Baseline characteristics were balanced between the two arms. The incidence of all grade of malaise and/or fatigue based on CTCAE for dex group was 53.6% and 58.3% for PLC group (p = 0.8119), that based on PRO CTCAE for dex was 47.2% and 59.3% for PLC (p = 0.3458). The incidence of ≥ grade 2 of malaise and/or fatigue based on CTCAE for dex group was 19.4% and 38.9% for PLC group (p = 0.0095), that based on PRO for dex was 27.8% and 52.8% for PLC (p = 0.0306). The most common AE during protocol period was hand foot skin reaction in both groups (75.6 % vs. 86.1%).

**Conclusions:** The KSCC1402/HGSG1402 study provided promising results that improve the supportive therapy for pts with REG-related fatigue and malaise. NCT02288078

**Legal entity responsible for the study:** Clinical Research Support Center Kyushu

**Funding:** Bayer Yakuhin, Ltd

**Disclosure:** S. Yuki: Honoraria: Taiho Pharmaceutical, Merck Serono, Bristol-Myers Squibb, Takeda Pharmaceutical, Chugai Pharmaceutical, Bayer Yakuhin, Eli Lilly Japan. Y. Komatsu: Taiho Pharmaceutical, Yakult Honsha, Chugai Pharmaceutical, Merck Serono, Pfizer Japan, Novartis Pharma, Ono Pharmaceutical, Daiichi Sankyo, Takeda Pharmaceutical, Eli Lilly Japan, Novartis Pharma, Daiichi Sankyo, Kuruba Corporation, E. Oki: Honoraria: Bayer Yakuhin. H. Baba: Honoraria: Bayer Yakuhin. All other authors have declared no conflicts of interest.
Background: Drug metabolism is genetically determined. Gender is one of the factors responsible for the large interpatient variability in the dose-effect relationship of cytotoxic drugs. Comparative data on the effect of gender on chemotherapy (CT)-related toxicity and tolerability are lacking in colon cancer.

Methods: This is a retrospective analysis of data from the PETACC-3 trial: 2974 pts (55.7% men (m) and 44.3% women (f)) with stage II and III colon cancer treated with fluorouracil/leucovorin alone (5FU/LV) or with irinotecan (FOLFIRI). Primary aim was to compare CT-related toxicity (according to NCIC-CTC-G) in m and f, and the increase of BAP independent of GC dose intensity, treatment regimens, durations, additive steroid usage, and FRAX® output. Now we plan the further study ESPRESSO-02 to investigate the efficacy of prevention GC induced osteoporosis in using GC premedication.

Results: From June 2013 to April 2015, 98 cases were enrolled, and 74 cases comprised the full analysis set. Not only the levels of BMD-LS but also those of total hip and femoral neck BMD at 16 weeks were decreased compared with baseline and the average percent changes were: -1.9% (n = 74, 95% CI -2.7% to -1.1%, p < .0001); -2.0% (n = 73, 95% CI -3.1% to -1.0%, p < .0001), respectively. Regarding secondary endpoints, there was no significant correlation between BMD change at baseline and baseline BMD status, GC dose intensity, primary site, treatment regimens, durations, additive steroid usage, and FRAX® output.

Conclusion: We found that periodic GC premedication caused the reduction of BMD. The increase of BAP independent of GC dose intensity, treatment regimens, durations, additive steroid usage, and FRAX® output. Now we plan the further study ESPRESSO-02 to investigate the efficacy of prevention GC induced osteoporosis in using GC premedication.

Clinical trial identification: University Hospital Medical Information Network (UMIN) Clinical Trials Registry (protocol ID UMIN000011054). Date of protocol fixation: May 7, 2013.

Legal entity responsible for the study: Hokkaido Gastrointestinal Cancer Study Group (HGCG)

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

FOLFOX after first progression from cetuximab plus FOLFIRI in molecularly selected, by NGS technique, metastatic colorectal (mCRC) pts. Few data are currently available on elderly population. This subgroup analysis evaluated the efficacy and safety of FOLFIRI plus cetuximab in age-defined pts subgroups.

Methods: A post hoc analysis was performed in CAPRI trial pts; outcomes (Progression Free Survival [PFS], Overall Response Rate [ORR], Safety) were analysed by age groups and stratified according to molecular characterization. Three age cut-offs were used to define elderly population (≥75 years; ≥70 years; ≥65 years). Median PFS was similar within the age subgroups in the intention to treat population, NGS cohort and quadruple WT pts, respectively. Likewise, ORR was not significantly different among age-subgroups in the three populations. Safety profile was acceptable and similarly reported among all age-groups, with the exception of grade ≥3 diarrhea (35% vs 25% p 0.04) and neutropenia (75% vs 37% p 0.03) in pts ≥75 years and grade ≥3 diarrhea (55% vs 25% p 0.04) and neutropenia (75% vs 37% p 0.03) in pts ≥75 years and grade ≥3 fatigue (31% vs 20 % p 0.01) in pts <75 years (Table).

Results: 349 mCRC pts were treated in first line with FOLFIRI plus cetuximab. Among those, 154 pts were aged more than 65 years, 86 over 70, 35 over 75. NGS was performed in 182 pts. Among them, 87 pts were aged more than 65 years, 46 over 70, 17 over 75. 104 of 182 pts were WT for KRAS, NRAS, BRAF, PIK3CA genes. In the quadruple WT group, 51 pts were ≥75 years; 26 were ≥70 years; 9 were ≥75 years. Median PFS was similar within the age subgroups in the intention to treat population, NGS cohort and quadruple WT pts, respectively. Likewise, ORR was not significantly different among age-subgroups in the three populations. Safety profile was acceptable and similarly reported among all age-groups, with the exception of grade ≥3 diarrhea (35% vs 25% p 0.04) and neutropenia (75% vs 37% p 0.03) in pts ≥75 years and grade ≥3 fatigue (31% vs 20% p 0.01) in pts <75 years (Table).

Conclusion: Tolerability of cetuximab plus FOLFIRI was acceptable in elderly pts. Similar ORR and PFS were observed according to age groups. No major differences in adverse events were reported among the defined subgroups.

Clinical trial identification: EudraCT 2009-01481-81

Legal entity responsible for the study: Department of Clinical and Experimental Medicine “F. Magrassi”, Second University of Naples, Italy

Funding: Merck Serono

Disclosure: All authors have declared no conflicts of interest.

A prospective observational study of the impact on bone metabolism of short-term periodic steroid premedication for chemotherapy for gastrointestinal cancer (ESPRESSO-01 study): pre-planned subgroup analysis


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Background: Although glucocorticoid (GC) premedication before chemotherapy are frequently used to prevent nausea and vomiting for continuing comfortable chemotherapy, the side effects of intermittent GCs on bone health have not yet been reported. We previously reported that GC premedication caused the reduction of bone mineral densities at lumbar spine (BMD-LS) and the increase of serum bone alkaline phosphatase (BAP) (ASCO GI 2016 Abst.523). We now report pre-planned subgroup results about this study (ESPRESSO-01 study).

Disclosures: The eligibility criteria were as follows: (i) histologically proven gastrointestinal cancer, (ii) The duration of periodical GC premedication is weekly, biweekly and triweekly; (iii) age over 20. The primary endpoint was to investigate the variations of BMD-LS by dexamethasone usage (BMD-DX), serum NTX, and BAP, between baseline and 16 weeks after starting chemotherapy. Secondary endpoints were the influence of GC dose intensity, treatment duration, regimens, primary site, and the WHO Fracture Risk Assessment Tool known as the FRAX® tool (http://www.shef.ac.uk/FRAX/).

Results: From June 2013 to April 2015, 98 cases were enrolled, and 74 cases comprised the full analysis set. Not only the levels of BMD-LS but also those of total hip and femoral neck BMD at 16 weeks were decreased compared with baseline and the average percent changes were: 1.9% (n = 74, 95% CI -2.7% to -1.1%, p < .0001); 2.0% (n = 73, 95% CI -3.1% to -1.0%, p < .0001), respectively. Regarding secondary endpoints, there was no significant correlation between BMD change at baseline and baseline BMD status, GC dose intensity, primary site, treatment regimens, durations, additive steroid usage, and FRAX® output.

Conclusion: We found that periodic GC premedication caused the reduction of BMD and the increase of BAP independent of GC dose intensity, treatment regimens, durations, additive steroid usage, and FRAX® output. Now we plan the further study ESPRESSO-02 to investigate the efficacy of prevention GC induced osteoporosis in using GC premedication.

Clinical trial identification: University Hospital Medical Information Network (UMIN) Clinical Trials Registry (protocol ID UMIN000011054). Date of protocol fixation: May 7, 2013.

Legal entity responsible for the study: Hokkaido Gastrointestinal Cancer Study Group (HGCG)

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Bevacizumab combined with 1st line chemotherapy in elderly patients (>75 years old) with metastatic colorectal cancer - interim results according to the chemotherapy regimen (CASSIOPEE)

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Background: Standard treatments of metastatic colorectal cancer (mCRC) have been studied in a limited number of elderly patients (pts) despite the increasing incidence of cancer due to population aging.

Methods: This ongoing prospective, multicenter non-interventional study, evaluates Bevacizumab combined with 1st line chemotherapy in elderly patients (>75 years-old) with metastatic colorectal cancer - interim results according to the chemotherapy regimen (CASSIOPEE)
Alfibercept plus FOLFIRI for 2nd line treatment of metastatic colorectal cancer (mCRC): Long-term safety observation from the global alfibercept safety and quality-of-life (OQL) program (ASQoP)


Background: The Ph 3 VELOUR study demonstrated that addition of aflibercept & FOLFIRI on d1 of a 2-wk cycle, until disease progression (PD), unacceptable toxicity, death or investigator/pt decision. Initial FOLFIRI dose & subsequent modifications were at physician’s discretion. Adverse events (AEs) were evaluated using CTCv4.03.

Conclusions: CASSIOPEIE provides an overview of a first line CTs pattern combined with BV in elderly patients with mCRC in daily French practice. Polychemotherapy was administered in nearly 70% pts. PFS and safety results are comparable to published randomized studies.

Clinical trial identification: Clinicaltrials.gov NCT01555762

Legal entity responsible for the study: N/A

Funding: Roche

Disclosure: L. Mineur: Advisory Board. P. Laplaige: Roche, Pfizer, Sanofi. All other authors have declared no conflicts of interest.

Adjunctive chemotherapy for stage III colorectal cancer in the elderly

D. Brunis1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1, D. Brungs1, E. Healey1, J. Rose1, T. Tubaro1, W. Ng2, W. Chua3, M. Carolan1

Background: Colorectal cancer (CRC) is a common and lethal malignancy which is related to aging, with almost 40% of CRC diagnosed above 75 years in both Australia and the USA. Aflibercept plus FOLFIRI for 2nd line treatment of metastatic colorectal cancer (mCRC): Long-term safety observation from...
Results: Patients in the 70yrs and older age group had poorer OS (5yr OS 58.8 vs 76.7%, HR 0.47 95% CI 0.31 – 0.70, p = 0.0013). After adjusting for TNM stage, perineural and lymphovascular invasion, completeness of resection, sex, and presence of a symptomatic primary, oxaliplatin combination chemotherapy continued to show a statistically significant improved OS in patients aged over 70yrs in the multivariate analysis (HR 0.54 95% CI 0.33 – 0.88, p = 0.009).

Conclusions: Patients 70yrs and older, with stage III colorectal, may gain a similar OS benefit with an oxaliplatin doublet chemotherapy as younger patients. Combination adjuvant chemotherapy should be considered in elderly patients

Legal entity responsible for the study: The Centre for Oncology Education and Research Translation (CONCERT)

Funding: The Centre for Oncology Education and Research Translation (CONCERT)

Disclosure: All authors have declared no conflicts of interest.

R. Lipp, M. Freibach, F. Freigang, P. Brecht
Wnte Research, GermanOncology GmbH, Hamburg, Germany

Background: Therapies with A-FOLFIRI in mCRC showed in up to a quarter of patients toxicity-related or patient-triggered discontinuations. The rationale of this study was to describe effects on treatment duration and compliance by using continuous recordings of PRO and defined toxicities under the real-world-conditions of oncological practices in Germany.

Methods: Patients with mCRC were assessed and analysed in 2 cohorts: cohort 1 with standardized requests for PRO (visual analog scale and QoL) and defined toxicities (diarrhea, hypertension, fatigue, infections) and cohort 2 without these requests. The patients were treated with a standard protocol of A-FOLFIRI in several therapy lines. The assignments for one of the cohorts were based on decisions of the oncologists.

Results: Data of n = 112 patients (44% women, 56% men, mean age 71.8 years) were sampled between Jan 2014 and Feb 2016 in 18 oncological practices. In cohort 1 n = 37 patients got requests for QoL, before start of every cycle and a diary for recording performance by VAS and specific toxicities. In cohort 2 n = 75 patients were guided based on standard oncologist’s practice. Qol. and VAS data were available in 81% and 67% and showed over all lines a maximal of 9.3 and 7.5 points, respectively. Over all lines A-FOLFIRI was administered for 8.3 cycles (58.8 weeks) in cohort 1 and 7.3 cycles (13 weeks) in cohort 2. An appearance of toxicities (≥3 CTCAE 4.0) was transmitted to the oncologist in a mean of 3.2 days. The rates of early discontinuations due to toxicities or patient’s wishes could be declined by 5.2% (13.1% cohort 1 vs 18.3% cohort 2) and dose reductions by 3.5% (17.3% cohort 1 vs 20.8% cohort 2).

Conclusions: In this cohort study requests for PRO and early intervention to toxicities showed in patients with mCRC under A-FOLFIRI a prolongation of the therapy and a delay or dose reduction by 5.2% (13.1% cohort 1 vs 18.3% cohort 2) and dose reductions by 3.5% (17.3% cohort 1 vs 20.8% cohort 2).

Legal entity responsible for the study: GermanOncology GmbH (Managing Director: Dr. Rainer Lipp)

Funding: GermanOncology GmbH

Disclosure: R. Lipp: Financial support of research project by Sanofi. All other authors have declared no conflicts of interest.
Evaluation of Charlson comorbidity index as predictor of survival in stage II-III colorectal cancer patients treated with surgery and neoadjuvant/adjuvant chemotherapy: A single Institution observational study

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Background: Comorbidity has a well documented detrimental effect on cancer survival, but it is difficult to disentangle its direct effect on survival from indirect effects via the influence on treatment choice. This study was aimed to assess the impact of comorbidity on survival in colorectal cancer (CRC) patients who underwent similarly aggressive treatment.

Methods: 236 CRC patients, 68 (29.6%) and 162 colon cancer (70.4%) treated with surgical resection and neoadjuvant/adjuvant chemotherapy from December 2002 to December 2008 at Humanitas Cancer Center were reviewed. The key independent variable was the Charlson Comorbidity Index (CCI) score. The differences between groups for categorical data were tested by the Chi-square test. Actuarial survival curves were generated using the Kaplan–Meier method.

Results: The median follow-up was of 113 months (range 8.2-145). The median age of patients was 63 (range 37.78). Since all patients had a diagnosis of non-colon cancer, the minimum CCI score was 2. In the univariate analysis CCI score, measured as a continuous variable, was significantly associated with poorer progression-free survival (PFS) (HR 1.65, 95%CI 1.52–1.80, p < 0.001), and overall survival (OS) (HR 1.55, 95%CI 1.41–1.71, p < 0.001). Patients who had a higher CCI score (>5) had a significantly poorer PFS and OS rates than did those with a CCI score of ≤5.

Additionally, in the multivariate analysis, factors associated with poorer outcome were stage (stage III versus stage II, p<0.029) and age (>70 years versus ≤70, p < 0.001). After adjusting for these factors we still observed a significant negative prognostic effect of CCI score on OS (adjusted HR for OS 1.65, 95%CI, 1.43–1.76, p < 0.001).

Conclusions: In this retrospective study we found that a higher CCI score is associated with poorer outcome providing convincing evidence that CCI score is an important negative prognostic factor even after adjusting for other prognostic factors. Some patients with comorbidity may forego chemotherapy unnecessarily, increasing avoidable cancer mortality.

Legal entity responsible for the study: Humanitas Clinical and Research Center

Funding: Humanitas Clinical and Research Center

Disclosure: All authors have declared no conflicts of interest.
Results: Mean age of Group A and B were 53.23 and 32.70 respectively (p=0.641). According to IIEF score, groups had some degree of ED, %42.9 and %57.1 (IIEF score 20.38 and 17.83) respectively (p=0.10). PN according to ITIEF were %21.7 (n=5) and %78.3 (n=18) (p=0.001), none of the patients had more than Grade 1 neuropathy.

Conclusions: These findings suggest that Osaippalin can cause peripheral neuropathy but not autonomic neuropathy such as ED. Further study and evaluation is necessary for exact decision. Therefore, the underlying pathology, either organic or psychological remains to be defined.

Legal entity responsible for the study: Pinar Dal

Funding: Eskişehir Osmangazi University Medical School

Disclosure: All authors have declared no conflicts of interest.

**560P** Patterns of venous thromboembolism risk in patients with localized colorectal cancer undergoing adjuvant chemotherapy or active surveillance

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Background: The risk of cancer-associated venous thromboembolism (VTE) is highly elevated in pts w/ metastatic colorectal cancer (CRC), and in particular during antineoplastic therapy. However, patterns of VTE risk in pts w/ localized CRC are unclear. Hence, we estimate the risk of VTE in CRC pts after curative surgery, and define its association with baseline risk factors, adjuvant chemotherapy (adCTx), disease recurrence, and death.

Methods: In this single-center historical cohort study, 562 pts w/ CRC (median age = 65.3 years; stages I, II, and III = 29, (5.2%), n = 160 (28.7%), n = 368 (66.1%); adCTx: n = 346 (61.7%) were included at the time of surgery and followed-up until the onset of VTE, disease recurrence, and death. The primary endpoint of this study was the cumulative incidence of objectively confirmed, symptomatic or incidental deep vein thrombosis and/or pulmonary embolism (VTE), accounting for death as a competing risk.

Results: During a median follow-up of 2.9 years, we observed 18 VTE events (3.2%), 142 recurrences (25.3%), and 52 pts (9.3%) died. The 6-month, 1-year, and 5-year risk of VTE was 1.4%, 1.8%, and 3.3%, respectively. In univariable time-to-VTE regression, adCTx was not associated with an increased risk of VTE (Subdistribution hazard ratio = 1.03, 95%CI: 0.40-2.66, p = 0.95). In multi-state analysis, the onset of disease recurrence emerged to be associated w/ an excessive increase in the risk of VTE (Transition hazard ratio (THR) = 11.8, 95%CI: 4.02-35.81, p < 0.0001). Conversely, the occurrence of VTE was associated with a 2.6-fold increase in the risk of disease recurrence (THR = 2.62, 95%CI: 1.07-6.42, p = 0.04).

Conclusions: The risk of VTE in pts w/ localized CRC undergoing curative surgery is very low. Importantly, adCTx does not appear to be a risk factor for VTE in this setting. Therefore, the role of primary thromboprophylaxis during adCTx is of low clinical benefit. The by far strongest determinant of VTE risk in curatively treated CRC pts turned out to be disease recurrence. Conversely, VTE emerged as a risk factor for recurrence, which indicates that VTE can be an early clinical sign for recurrent disease in this patient population.

Legal entity responsible for the study: Medical University of Graz

Funding: Medical University of Graz

Disclosure: All authors have declared no conflicts of interest.

**561P** Molecular, clinical and prognostic characterization of double KRAS/PIK3CA (dKP) mutated metastatic colorectal cancer (mCRC)

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Background: Molecular screening in mCRC has demonstrated an impact in treatment selection and outcome estimation. KRAS mutations (mut) frequently coexist with PIK3CA mut. Molecular, clinical and prognostic association of the dKP group has not been studied in detail.

Methods: 657 mCRC patient records that were eligible for targeted mut profile were reviewed. From Jan 2010 – Jan 2014, mass spectrometry (sequenom oncocene panel) was performed in 497 samples, and from Jul 2014 – Jul 2015, next generation sequencing (MiSeq amplicon oncogene and tumor suppressor panel) in 160.

Results: dKP mut were found in 82 cases (12.5%), RAS/BRAF/PIK3CA wild type (wt) in 38.4%, RAS mut/PIK3CA wt 38.5%, RAS/BRAF wt/PIK3CA mut 3.4% and BRAF mut 7.2%. PIK3CA mut are enriched in KRAS mut as compared to RAS wt (25% vs. 9%, OR = 3.4, p < 0.001). KRAS mut in dKP were less likely to codon 13 as compared to only KRAS mut (9% vs. 19%, OR = 0.43, p = 0.07). PIK3CA codon mut distribution in dKP was different from non-dKP, less frequently of kinase domain (17% versus 26%, OR = 0.6, p = 0.4) and more likely of rare domains (9% versus 4%, OR = 2.1, p = 0.6). dKP and co-existing TP53 mut as compared to non-dKP (51% vs. 65%, OR = 0.24, p < 0.01). Tumor site in dKP was 43% right side, 39% left and 18% rectum. Metastasis (mts) location at diagnosis was different, peritoneal disease was more frequently seen in BRAF mut and dKP as compared to others (35% and 27% vs. 15%). In multivariate model that includes number and location of mts, mts resection, tumor site and mut profile, RAS mut had significantly worse time from recurrence to death (TRD) as compared to RAS/BRAF/PIK3CA wt (HR 1.4, CI95% 1.1-1.9), a similar trend was observed for dKP (HR 1.3, CI95% 0.8-2.0). In univariate model, TRD estimates of dKP were not significantly different from RAS mt (HR = 1.0, CI95% 0.7-1.3).

Conclusions: The molecular features of dKP samples such as enrichment in particular KRAS/BRAF/PIK3CA codons, less co-existing TP53 mut, together with their particular clinical characteristics suggest that the biology of these tumors is different from other genomically-defined groups. Nevertheless, co-occurrence of a PIK3CA mut on top of RAS mut does not significantly impact survival in the metastatic setting.

Legal entity responsible for the study: N/A

Funding: VHI

Disclosure: J. Tabernero Consultant/Advisory role: Aman, Bayer, Boehringer Ingelheim, Glaxo, Chugai, Lilly, MSD, Merck Serono, Novartis, Roche, Sanoﬁ, Symphogen, Takeda, Taiho. All other authors have declared no conflicts of interest.

**561P** CDX2 loss as a prognostic and predictive biomarker in metastatic colorectal cancer

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Background: While the lack of CDX2 expression has recently been proposed as a potential biomarker for high relapse risk in patients with stage II and III colon cancer after complete surgical resection, its role in metastatic colorectal cancer (CRC) remains unclear.

We conducted a retrospective analysis to characterize the clinicopathologic features of CDX2-negative metastatic CRC, and to assess the value of CDX2 loss as a potential prognostic and predictive biomarker for metastatic CRC.

Methods: We identified 66 patients with CDX2-negative metastatic CRC treated at our institution between 2006 and 2016, as well as a comparison cohort consisting of 79 patients with CDX2-positive metastatic CRC. Overall survival (OS) and progression-free survival (PFS) for first line systemic therapy were estimated using the Kaplan-Meier method. The associations of CDX2 expression with survival were evaluated using Cox proportional hazards regression models.

Results: The prevalence of CDX2 loss in our cohort was 5.6%. Patients with CDX2-negative metastatic CRC were significantly more likely to be female (62% vs. 44%, p = 0.03), have right-sided primary tumors (55% vs. 34%, p = 0.01) of poorly-differentiated histology (55% vs. 24%, p < 0.0001), with distant lymph node metastasis (47% vs. 16%, p = 0.0001). The median OS for CDX2-negative and positive metastatic CRC patients were 8 months and 39 months, respectively (HR = 0.94, CI 95% 2.49-4.54, p = 0.0001). After adjusting for covariates that are significant in a multivariate model including age, sex, tumor grade, and the presence of BRAF mutation, the association of CDX2 loss and OS remained statistically significant (HR = 4.52, CI 95% 2.50-8.17, p < 0.0001). In addition, the objective response rate (29% vs. 68%, p = 0.0001) and median PFS (3 vs. 10 months, HR 2.23, CI 95% 1.52-3.27, p < 0.0001) for first line chemotherapy were significantly decreased in CDX2-negative metastatic CRC patients.

Conclusions: CDX2 loss in metastatic CRC is an adverse prognostic feature and a negative predictor of response to chemotherapy. These promising results warrant validation in an independent cohort. In addition, future clinical trials should be considered to evaluate the optimal treatment strategy for this aggressive histology.

Legal entity responsible for the study: Mayo Clinic

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Disclosure: All authors have declared no conflicts of interest.
Genomic instability and early-onset colorectal cancer: a new form of classifying the disease?


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Background: Early-onset colorectal cancer (EOCRC) is an uncommon entity frequently associated with poor clinical outcomes. Therefore, advances in the understanding of its molecular basis are essential for the adequate management of the patients.

Methods: We used a high-resolution array comparative genomic hybridization (aCGH) platform to investigate the chromosomal instability (CIN) of 60 EOCRC (<45 years at diagnosis), and submitted the data to an unsupervised hierarchical clustering analysis in order to unveil possible associations between the CIN profile and the clinical features of the tumors. We also evaluated the microsatellite instability (MSI) and CpG island methylator phenotype (CIMP) statuses with the aim of investigating a possible relationship between CIMP, MSI and CIN.

Results: Based on the similarity of the copy number alteration (CNAs), the unsupervised analysis stratified samples into two main clusters (A, B) and four secondary clusters (A1, A2, B1, B4). We observed a correspondence with the molecular classification of colorectal cancer, in such a way that the CIMP-High tumors were mostly contained in A1 or A2 depending on the CIN degree (with microsatellite and chromosome stable tumors [MACS, 1-3 whole chromosomes affected] mainly included in A1 and CIN- tumors [none whole chromosome affected] mainly included in A2), and the CIMP-Low/0 tumors were mostly contained in B3 or B4 depending on the presence/absence of MSI. Interestingly, each subcluster showed some distinctive clinicopathological features. But more interestingly, the CIN of each subcluster mainly affected particular chromosomes, providing evidence of the association between the three indicators of genomic instability evaluated.

Conclusions: We observed a correlation between the CIMP/MSI/CIN statuses in EOCRC which enabled us to outline an algorithm whereby tumors could be categorized according to these features. Our findings may provide a basis for a new form of classifying EOCRC according to the genomic status of the tumors.

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Disclosure: All authors have declared no conflicts of interest.

Clinical significance of thymidine kinase 1 expression on TAS-102 treatment in RECURSE phase III trial of TAS-102 versus placebo for metastatic colorectal cancer


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Background: TAS-102 is an oral nucleoside antitumor agent, consisting of trifluoride (FTD) and tipiracil hydrochloride. FTD is incorporated into DNA after phosphorylation by thymidine kinase 1 (TK1). In the RECURSE Phase III, an overall survival (OS) benefit for TAS-102 over placebo was observed in the overall population and was consistent with that in 266 Japanese patients (pts) (TAS-102 vs. placebo; 7.8M vs 6.7M, HR = 0.77). Correlations between TK1 expression and OS, progression-free survival (PFS) and disease control rate (DCR), were investigated.

Methods: Immunohistochemical analysis of TK1 expression in cytoplasm was blindly assessed. TK1 expression was divided into high or low according to the cut-off points at each 5% increment of occupancy of positive cells previously reported (4265, ESMO 2013).

Results: 179 FFPE archival tumor tissues from 183 additional consenting Japanese pts were evaluable for TK1 expression. The median OS with a high TK1 expression tends to shorter than that with a low TK1 in the placebo group, whereas TAS-102 tended to reduce the risk of death at each cut-off point in pts with a high TK1 without a statistical significance (Table). In addition, OS benefit was more pronounced in pts with a high TK1 at cut-off point of 10% or 15%. Conclusions: TK1 could be a negative prognostic factor of mCRC and some OS benefit for TAS-102 was observed in pts with a high TK1. Further investigation is needed to clarify the clinical significance of TK1 expression on TAS-102 treatment since this study included a small number of pts. The PFS and DCR are presented in this meeting.

Table: 563P

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<td>≤70yrs</td>
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<tr>
<td>MSH2/MSH6</td>
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Legal entity responsible for the study: Taiho Pharmaceutical Co., Ltd.

Funding: Taiho Pharmaceutical Co., Ltd.
Disclosure: K. Yamazaki, Y. Komatsu, K. Yamaguchi: Honoraria (lecture fee) from Taiho Pharmaceutical Co., Ltd. T. Yoshino: Corporate-sponsored Research: Research funding from GlaxoSmithKline K.K., Boehringer Ingelheim GmbH. T. Tanase: Employee of Taiho Pharmaceutical Co., Ltd. Stocks of Otsuka Holdings Co., Ltd. All other authors have declared no conflicts of interest.

The impact of mass spectrometry multiplex platform on the management of metastatic colorectal patients

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Background: Molecular testing is becoming an important part of the diagnosis of any patient with cancer. The challenge to laboratories is to meet this need, using reliable methods and processes to ensure that patients receive a timely and accurate report on which their treatment will be based. The aim of this abstract is to analyzed the benefit of the introduction in the clinical practice of a multiplex platform on the management of metastatic colorectal cancer (CRC).

Methods: DNA extraction by BioOstic Tissue DNA Isolation kit from tumor after microdissection (>20% tumoral cells). k-ras exon 2 mutations by Sanger sequencing in 277 CRC, by pyrosequencing (KRAS status, Diatech Pharmacogenetics) in 538 CRC; n-ras and b-raf mutations by pyrosequencing (NRAS and BRAF status, Diatech Pharmacogenetics) only in k-ras wt CRC from 01/2014. K-ras, n-ras, b-raf and pik3ca mutations by Maldi-TOF Mass Spectrometry (MassArray Agena Bioscence) with Myriapod Colon Status (Diatech Pharmacogenetics) only in k-ras wt CRC from 01/2014. K-ras, n-ras, b-raf and pik3ca mutations in all patients with CRC, avoiding the step by step analysis approach constrained by a single method. For all genes the change of methodology has improved the diagnostic sensitivity of test. The introduction of multiplex platform allowed the simultaneous analysis of k-ras, n-ras, b-raf and pik3ca mutations in all patients with CRC, avoiding the step by step analysis approach constrained by a single gene methodology. The comparison of technical features is listed in the table.

Results: The mutations frequencies were 41.5% k-ras by Sanger sequencing; 46.1% k-ras by pyrosequencing (KRAS status, Diatech Pharmacogenetics) only in k-ras wt CRC from 01/2014. k-ras, n-ras, b-raf and pik3ca mutations by Maldi-TOF Mass Spectrometry (MassArray Agena Bioscence) with Myriapod Colon Status (Diatech Pharmacogenetics) only in k-ras wt CRC from 01/2014.

Conclusions: The introduction in the routine diagnostics of a multiplex platform is clearly an attractive approach to increase the quality and the rapidity of molecular analysis results, that can be translate in a better clinical management of metastatic colorectal patient.

Legal entity responsible for the study: Humanitas Research Hospital

Funding: National Health System

A systematic review and meta-analysis of the prognostic value of total cell-free DNA quantification in metastatic colorectal cancer


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Background: Circulating DNA is a mixture of DNA from normal and tumor cells. The majority of studies analyzes the clinical potential of tumor specific mutations which are detectable in a fraction of patients. In contrast, the total cell-free DNA (cfDNA) can be analyzed in all patients and a normal upper limit provided for standardization. Studies suggest that levels of total cfDNA are higher in CRC than healthy controls and associated with a poor prognosis in metastatic disease. This indicates a strong clinical potential calling for statistical validation. The aim was to perform a systematic review and meta-analysis of the prognostic value of total cfDNA in patients with metastatic colorectal cancer (mCRC) treated with chemotherapy.

Methods: A systematic literature search of PubMed and Embase was performed by two independent investigators (KGS and AKB). Eligibility criteria were: total cfDNA analysis, mCRC, prognostic value during palliative treatment. The PRISMA guidelines were followed, and meta-analysis applied on both aggregate data extraction and individual patients’ data provided by the authors when applicable. Primary endpoint was overall survival (OS).

Results: A total of 11 patient cohorts were identified, including a total of 1158 patients. The majority of data were based on patients with late-line disease, but also a cohort of 86 patients in second-line, and study in the first-line settings, with similar results. Seven studies used qPCR methods, two BEAMing technology and two digital droplet PCR. The baseline median levels of cfDNA was similar in the presented studies, and all individual studies reported a clear prognostic value in favor of patients with lowest levels of baseline cfDNA. The meta-analysis revealed a combined estimate of favorable overall survival hazard ratio (HR) in patients with levels below the median cfDNA (HR = 2.46, 95% CI 2.17-2.75, p < 0.0001).

Conclusions: The total cfDNA levels are high in patients with mCRC and bear strong prognostic information, which should be tested prospectively by using a pre-defined cut-off value. Total cfDNA can be measured in a simple pre-treatment blood sample and potentially aid in clinical decision-making.

Legal entity responsible for the study: N/A
The differences between suspicious Lynch and sporadic dMMR colorectal cancers

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Background: Few studies have systematically compared the difference between germline and sporadic dMMR colorectal cancers on clinical-pathological features, prognosis, lymphocytic reactions, somatic mutation frequencies and neoantigen burdens. Methods: We retrospectively collected dMMR colorectal patients identified by postoperative immunohistochemistry screening. According to genetic test or clinical-pathological criterions, patients were then grouped as suspicious Lynch or sporadic dMMR. We compared the clinico-pathologic and prognostic differences between the two groups. By evaluating the four components of lymphocytic reaction (i.e., C3h-like reaction (CBO), immunoreactions in the invasive margin (IM), in the tumour stroma (TS) and cancer center (CC)) and counting CD3+, CD4+, CD8+, FoxP3+ tumor-infiltrating lymphocytes, we investigated their immune response and lymphocyte subgroup differences. By whole genome sequencing and neoantigen detection pipeline, we contrasted their discrepancies on mutational frequencies and neoantigen burdens.

Results: 213 of the 381 dMMR pts were grouped: 94 sporadic dMMR and 119 suspicious Lynch. Sporadic-dMMR patients were significantly older (P = 0.001), had more tumor progression to splenic flexure (P < 0.001) and with postoperative chemotherapy (P < 0.005). The OS rate was higher in suspicious Lynch group (P = 0.006), after adjustment for ages and chemotherapies, the differences still remained significant (P < 0.007). The scores of CBO (P = 0.013), IM (P = 0.044) and total immunoreactions (P = 0.036) of suspicious Lynch group is significantly higher. The number of CD3+, CD4+, CD8+, FoxP3+ lymphocytes in CC, CD3+, CD4+, FoxP3+ lymphocytes in TS, CD3+, FoxP3+ lymphocytes in IM of suspicious Lynch patients were significantly more. There were also more somatic mutations and neoantigen burdens in suspicious Lynch group compared to sporadic dMMR group, with significant difference (357/pt vs 66/pt, P = 0.015; 588/pt vs 91/pt, P = 0.049). Conclusion: There were more somatic mutations and neoantigens in suspicious Lynch patients and causing their more intense immunoreactions, which might benefit their survival.

Legal entity responsible for the study: Sun Yat-sen University Cancer Center

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Disclosure: All authors have declared no conflicts of interest.

BRAF mutated metastatic colorectal cancers do not always possess poor clinical outcome

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Background: BRAF mutated (mBRAF) metastatic colorectal cancers (mCRC) are known to be related poor prognosis and low response to current chemotherapy. We investigated clinical outcomes of unselected mBRAF mCRC patients (pts) treated in real clinical practice.

Methods: A total of 125 pts with mBRAF mCRC were treated between Jan 2005 and OCT 2015 at Asan Medical Center. We analyzed clinical outcomes, such as survival and progression free survival after 1st (PF1), 2nd (PF2), and 3rd (PF3) line chemotherapy, of these pts using mCRC registry data of our center. Results: Of 125 tumors, 121 had BRAF mutation of V600E, 3 of K600IE, 1 of V600E and K600E. Median age was 59 years old and 70 (56.0%) pts were male. Primary tumor was located in right colon in 60 (48.0%) pts, left colon in 43 (34.4%) pts, and rectum in 22 (17.6%) pts. KRAS exon 2 mutation was tested in all pts; 122 had no mutation, while 3 had co-mutation of KRAS. NRAS mutation was tested in 29 pts, and rectum in 22 (17.6%) pts. KRAS wild-type colorectal cancer treated with anti-EGFR therapy. BRAF and PIK3CA mutations are known to affect a response in anti-EGFR therapy. However, the relationship between the prevalence of BRAF/PIK3CA mutations and the location of the primary site is still unclear.

Methods: We prospectively collected tumor samples and clinical data from colorectal cancer patients in 14 hospitals and investigated KRAS/NRAS/BRAF/PIK3CA gene mutations, including 33 types of BRAF non-V600E mutations, using a PCR-based multiplex kit.

Results: As of April 30, 2015, a total of 545 CRC pts were enrolled, and 313 patients (57%) revealed KRAS/NRAS wild-type cancer. Patient characteristics included: median age, 65 (range, 30–90); male/female, 46%/54%; clinical stage I–III/IV, 15%/85%; and location of primary site, right-sided colon/left-sided colon/rectum, 23%/30%/47%. The prevalence of BRAF V600E/BRAF non-V600E/PIK3CA mutations were 10.1%, 4.7%, and 5.9%, respectively. The detected BRAF non-V600E mutations were G466E, G469A, N581T, D584G, T599V, 600insT, V600R, K601E and K601N. All mutations were mutually exclusive. In RAS wild-type cancer patients, BRAF/PIK3CA mutations were more frequent in female (p = 0.0029), right-sided (p = 0.0001) and peritoneal metastasis (p < 0.0016) cases and less frequent in cases presenting liver metastasis (p = 0.0084). In RAS wild-type right-sided cancers, the prevalence of BRAF V600E/BRAF non-V600E/PIK3CA mutations were 31.7%, 8.1% and 19.2%, while in left-sided colon and rectum cancers, they were 4.6%, 2.5% and 3.6%, respectively. Conclusion: More than half of RAS wild-type right-sided colon cancer patients have BRAF/PIK3CA mutations, including BRAF non-V600E. The existence of these mutations may affect anti-EGFR efficacy between right- and left-sided colorectal cancers.

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

Diagnostic value of methylation status of T-UCRs for colorectal cancer

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1Clinical and Molecular Oncology Laboratory, Medical School, University of Patras, Patras, Greece, 2Division of Transcribed Ultra Conserved Regions (T-UCRs) is often disregulated in various types of cancer. Regulation of T-UCR expression includes epigenetic mechanisms, and in particular CpG island methylation. These T-UCRs (160, 283 and 346) have been found to be methylated in colon adenocarcinomas. The present study assesses the use of the T-UCR methylation status in circulating DNA as a diagnostic marker for colorectal cancer (CRC).

Methods: Expression and methylation levels of T-UCRs 160, 283 and 346 were assessed in neoplastic and paired normal colonic fresh frozen tissue specimens from 75 CRC patients, as well as in 5 fresh frozen adenoma tissue specimens. Methylation status of the three T-UCRs was also determined in plasma from 161 patients (56 CRC patients, 55 adenoma patients, 40 healthy subjects and 10 patients with colon inflammation or diverticulosis).

References:

1. A. Koteromba1, A. Antonacopoulou1, F.-I. Dimitrakopoulos2, G. Diamantopoulou2, T. Themelisopoulos2, C. Oikonomou3, I. Kouloukou3, D. Dalla3, P. Karatasou2, E. Katsakoulis2, A. Koutras1, T. Makatsoris1, M. Stavropoulos4, K. Thomopoulos5, H. Kallionis1, 1Clinical and Molecular Oncology Laboratory, Medical School, University of Patras, Patras, Greece, 2Department of Surgery, University of Patras, Patras, Greece, 3Division of Clinical Oncology, University Hospital Patras, Patras, Greece, 4Department of Gastroenterology, Medical School, University of Patras, Patras, Greece, 5Division of Gastroenterology, University Hospital Patras, Patras, Greece

Background: Expression of Transcribed Ultra Conserved Regions (T-UCRs) is often disregulated in various types of cancer. Regulation of T-UCR expression includes epigenetic mechanisms, and in particular CpG island methylation. These T-UCRs (160, 283 and 346) have been found to be methylated in colon adenocarcinomas. The present study assesses the use of the T-UCR methylation status in circulating DNA as a diagnostic marker for colorectal cancer (CRC).

Methods: Expression and methylation levels of T-UCRs 160, 283 and 346 were assessed in neoplastic and paired normal colonic fresh frozen tissue specimens from 75 CRC patients, as well as in 5 fresh frozen adenoma tissue specimens. Methylation status of the three T-UCRs was also determined in plasma from 161 patients (56 CRC patients, 55 adenoma patients, 40 healthy subjects and 10 patients with colon inflammation or diverticulosis).
Results: Expression levels of all three T-UCRs were lower in neoplastic tissues, compared to normal adjacent colonic tissues, but only in T-UCR 160 the difference was statistically significant (p < 0.001). Methylation levels of 160, 283 and 346 were higher in colorectal cancer tissues compared to normal adjacent tissues (p < 0.001, p = 0.029 and p = 0.000 respectively). Notably, methylation levels of 160 and 346 in adenomas were higher than those in normal tissues but lower than in those cancer tissues. Methylation status of 160 in plasma differed significantly among the four different groups (p = 0.0241) and the difference increased when we compared the methylation status in colorectal adenoma and adenocarcinoma patients with healthy subjects or patients with inflammation or diverticulosis (p = 0.007). When methylation status was used to predict if a subject has colorectal adenocarcinoma, specificity and sensitivity were 85% and 30% respectively.

Conclusions: Methylation of T-UCR 160 in plasma has great specificity for CRC but low sensitivity. Alteration of the methodological approaches to improve the sensitivity could result in a promising non-invasive screening method for CRC.

Legal entity responsible for the study: University of Patras

Funding: University of Patras

Disclosure: T. Makatositis: Travel Pfizer, Roche, Astellas. Advisory: Roche, Boehringer. Honoria: Roche, Sanofi, Merck, Amgen, H. Kalofoinos: Travel: Pfizer, Roche, Novartis, Elioraxis Advisory: Roche, Novartis, MSD. Generation, Pfizer, Lilly, Leo, Amgen, Janssen, Merck, Merck Sermo. Research Funding: Roche, Novartis, MSD, Generation, Pfizer, Lilly, Bayer, Amgen, Janssen, Merck Sermo. All authors have declared no conflicts of interest.

Abstracts Annals of Oncology
Background: Whole blood mRNA expressions have been proposed as useful prognostic biomarkers in patients with cancer. Few studies have evaluated circulating mRNAs in patients with metastatic colorectal cancer (mCRC). Our objective was to find prognostic mRNAs in patients with mCRC treated with 3rd line cetuximab and irinotecan.

Methods: In a prospective Phase 2 study, whole blood samples were collected in PAXgene RNA tubes from 104 mCRC patients. The samples were collected before 3rd line treatment with irinotecan and cetuximab every second week. All patients had, prior to inclusion, progressed on 5FU and oxaliplatin. RNA was purified from the whole blood and hybridized to Affymetrix U133plus2 microarrays. Cox models were used and only mRNAs, adjusted with the Bonferroni method, were retained.

Results: We found that eight of the tested mRNAs had a Bonferroni adjusted p-value < 0.05 and were retained for further analysis. An eight-mRNA risk index for overall survival (OS) was composed. When dichotomized in high and low risk by using the risk index’s median, a hazard ratio (HR) of 4.96 (CI 95% 3.04-8.1) p-value = 2x10 ^ -10 was found. In the subgroup of KRAS wt patients a 16-gene risk index was significant for OS (HR = 5.87, CI 95% 3.08-11.2; p-value = 7x10 ^ -7). In multivariate analyses, adjusting for hemoglobin, white blood cells, absolute neutrophil count, platelets, age and performance status, the risk index remained significant (HR = 7.19, CI 95% 3.35-15.4 and HR = 7.79, CI 95% 2.7-22.9) for all patients and KRAS wt patients respectively.

Conclusions: Our results showed an eight-mRNA risk index as prognostic for OS in patients with mCRC. Thus using mRNAs in whole blood, which is non-invasive and can be repeated throughout a treatment period, has prognostic potential as a biomarker in the clinical setting if validated in the future.

Legal entity responsible for the study: Herlev and Gentofte Hospital

Disclosure: P. Pfeiffer: Research funding: Merck Serono, Roche, Taiho, Amgen.

P. Pfeiffer: Research funding: Merck Serono, Roche, Taiho, Amgen. All other authors have declared no conflicts of interest.

57/P Gene expression profile reveals a nodal status signature in rectal carcinomas

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Funding: INCISO (FAPESP 2008/57887 and CNPq 573589/09-9) and FAPESP (2014/06323-9).

Disclosure: All authors have declared no conflicts of interest.

57/P Perineural invasion as a prognostic factor in rectal cancer treated with preoperative chemoradiotherapy: A multicenter retrospective study


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Background: Preoperative chemoradiotherapy is used as a standard treatment in locally advanced rectal cancer. Perineural invasion has been suggested as a poor prognostic factor in colorectal cancer. However, the prognostic role of perineural invasion for rectal cancer after preoperative chemoradiotherapy is not well studied in the UNF group compared with the F prognosis group (fold change magnitude: range -2.5 +3.5), 42 genes belonging to the olfactory pathways, were not considered. Among 66 remaining genes, 19 were pseudogenes, 7 uncharacterized non-coding RNA, 4 involved in the immune response and one was a miRNA (MIR4481). All these genes were upregulated. Further 9 genes were cancer-related (6 up and 3 downregulated). The remaining genes (n = 26), most of which involved in key cellular processes, have not yet been associated with cancer and/or cancer prognosis. Differential expression of 14 out of 16 selected genes was validated, e.g. CETF1 and ROR2 involved in cell adhesion and in Wnt pathway, respectively.

Conclusions: Stage III CRC pts with F and UF prognosis following adjuv CHT differs at a transcriptomic level. These findings may have important implications for FP-based adjuv CHT.

Legal entity responsible for the study: University of Florence

Funding: Istituto Toscano Tumori (Florence) - Ente Cassa di Risparmio di Firenze (Florence)

Disclosure: All authors have declared no conflicts of interest.

Table: 57/P

<table>
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<tr>
<th>Index for OS</th>
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<th>HR</th>
<th>CI 95%</th>
<th>p-value</th>
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<tr>
<td>8-mRNA risk index</td>
<td>All patients</td>
<td>4.96</td>
<td>3.04-8.1</td>
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<tr>
<td>16-mRNA risk index</td>
<td>KRAS wt patients</td>
<td>5.87</td>
<td>3.08-11.2</td>
<td>7x10 ^ -7</td>
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</tbody>
</table>

57/P A transcriptomic profile predicts clinical outcome in stage III colorectal cancer patients treated with adjuvant chemotherapy

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Background: 5-year overall survival of stage III colorectal cancer (CRC) patients (pts) treated with standard adjuvant (adjuv) chemotherapy (CHT) (a fluoropyrimidine, FP +/- oxaliplatin, OHP) is still unsatisfactory and highly variable (42-88%). Although in CRC single molecular biomarkers or molecular signatures predictive of adjuv CHT outcome have been identified, none of them has been validated. The goal of this study was to identify and validate molecular biomarkers predictive of response to FP-based adjuv CHT in stage III CRC pts.

Methods: From a large case series of CRC pts who received adjuv CHT (a FP +/- OHP) we selected two groups with favorable (F) (no evidence of disease recurrence (DR) within 5 yrs from CHT, n = 12) or unfavorable (UNF) (evidence of DR within 3 yrs from CHT, n = 12) prognosis. We used fresh frozen CRC explants according to an IRB approved protocol. Global gene expression profile was performed by Ion Proton Software (Affymetrix). Differentially expressed genes in relation to lymph node status were assessed using BRB array tools software, establishing a two-tailed p-value < 0.001 with low false discovery rate ratio (FDR) < 20% as significant. Molecular function and biological processes were evaluated using Panther classification system (Gene Ontology Reference Genome Project).

Results: Five of 33 patients presented lymph node positivity. A signature of 88 coding transcripts was able to differentiate the cases according to lymph node status after surgery. Among these genes, a set of histones (HIST1H4I, HIST1H2BK, HIST1H2B), HIST1H13F, HIST1H2BD, H2AFX) was overexpressed in patients with positive nodal status. These cases also presented no pathological response to chemoradiotherapy and worse prognosis features. Additional differentially expressed transcripts were also related to chromatin assembly and disassembly and to nucleic acid binding.

Conclusions: The regulation of chromatin condensation is a putative mechanism associated with response to treatment as well as with lymph node positivity prediction in rectal cancer samples. More important, the discrepancy in nuclear structure regulation could be detected upon diagnosis, which can be used as a tool to predict outcomes and design new treatment strategies for rectal cancer patients.

Legal entity responsible for the study: Silvia Regina Rogatto

Funding: INCISO (FAPESP 2008/57887 and CNPq 573589/09-9) and FAPESP (2014/06323-9).

Disclosure: All authors have declared no conflicts of interest.
multicenter data. The aim of this study is to evaluate the prognostic impact of perineural invasion in rectal cancer treated with preoperative chemoradiotherapy.

Methods: From Jan 2002 to Dec 2010, 1260 patients, with locally advanced rectal cancer treated with preoperative chemoradiotherapy at three institutions, were included. The median radiation dose was 5040 cGy with concurrent chemotherapy. Their medical charts were retrospectively reviewed including pathology report. Survival analysis was performed to identify the clinicopathologic factor affecting disease-free survival (DFS) and overall survival (OS).

Results: Perineural invasion was positive in 221 patients (17.5%). The patients with perineural invasion were associated with more advanced pathologic stage, less tumor regression grade, more circumferential resection involvement, more positive lymphatic invasion, and more positive venous invasion. The DFS and OS of the perineural invasion positive patients was significantly poorer than that of the perineural invasion negative patients (5-year DFS: 46.5% vs 81.1%, p < 0.001; 5-year OS: 62.5% vs 90.2%, p < 0.001). Multivariate analyses, using the Cox proportional hazards model, indicated that perineural invasion (hazard ratio [HR] = 1.95; 95% CI = 1.45-2.62, p < 0.001), age, yp stage and circumferential resection were prognostic factors for disease-free survival. Perineural invasion (HR = 1.95; 95% CI = 1.35-2.82, p < 0.001), age, gender, tumor regression grade, yp stage of CFR in patients with newly diagnosed adenocarcinoma chemotherapy were independently significant risk factors for overall survival in multivariable analysis.

Conclusions: Perineural invasion was associated with poor DFS and OS in rectal cancer patients who undergo preoperative chemoradiotherapy. These patients require careful monitoring after surgery.

Legal entity responsible for the study: H Won Park

Funding: Seoul National University Hospital

Disclosure: All authors have declared no conflicts of interest.

A nomogram for predicting overall survival (OS) in Japanese patients (pts) with advanced colorectal cancer (aCRC) treated with irinotecan (IRI)-based regimens


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Background: One of the standard treatments for aCRC is IRI-based regimens, which are commonly used as second line treatment in Japan. We conducted a prospective observational study to examine the correlation between UGT1A1 genotypes and the clinical outcome of IRI-based regimens in Japanese pts with aCRC (NCT01399516). We presented previously the results of OS, the secondary endpoint (ASCO 2015, Abst No. 3523). Furthermore, We are going to present update results of OS (ASCO 2016, Abst No. 3571). We developed a nomogram for predicting survival of pts treated with second-line IRI-based regimens after first-line oxaliplatin-based treatment.

Methods: From Oct 2009 to Mar 2012, 1,376 pts with histologically confirmed aCRC treated with IRI-based regimens were enrolled to the study. Along all enrolled pts, 747 pts were treated with the second-line IRI-based regimens after first-line oxaliplatin-based treatment. A nomogram for predicting OS was developed using multivariable Cox proportional hazards model. The discriminative ability and predictive accuracy of the nomogram were determined by concordance index (c-index) and calibration plot. The nomogram was internally validated using bootstrap resampling.

Results: The median OS was 18.5 months (95% CI: 16.8 – 20.7). The multivariable Cox proportional hazards model included age, performance status, resection of primary tumor, location of primary tumor (right vs left), tumor burden based on longitudinal diameters of target lesions according to the RECIST criteria, diabetes and white blood cell count as predictors of OS. The resulting nomogram demonstrated good discrimination and calibration in predicting OS, with a bootstrap-corrected c-index of 0.68. The nomogram showed good separation between risk groups stratified by tertile of the total score, with median OS of 10.1, 18.6, and 29.4 months for low, middle, and high risk groups, respectively.

Conclusions: This proposed nomogram is well calibrated and internally validated. External validation is essential before implementing this nomogram in clinical practice.


Legal entity responsible for the study: Daichi Sankyo

Funding: Daichi Sankyo


Risk factors for brain metastases in patients with metastatic colorectal cancer


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Background: Brain metastases (BM) from colorectal cancer (CRC) are rare and usually develop late in the disease. However, it has been suggested that more patients will be diagnosed with BM from CRC due to improved diagnostics and increased survival. The
aim of this study was to identify biological and clinical characteristics that could predict later BM development in long surviving patient with metastatic (m) CRC.

Methods: We retrospectively reviewed a multicenter database and biobank encompassing consecutive patients with mCRC who all received cetuximab in combination with irinotecan as third-line treatment independently of RAS status between 2005 and 2008. We performed RAS (KRAS & NRAS), BRAF, and PIK3CA sequencing of DNA from primary tumor tissue.

Results: Totally, 480 patients were included in the study. BM were diagnosed in 42 patients (8.8 %) at median 29 months after mCRC diagnosis. Patient characteristics are shown in table 1. Patients with BM had a significantly longer survival from mCRC diagnosis than non-BM patients (32 months vs 28 months, p = 0.001). On univariate cox regression analysis the risk of developing BM was increased in patients with rectal cancer (Hazard ratio (HR) = 2.478, p = 0.005), metastatic disease status (HR = 2.296, p = 0.003), and lung metastases at mCRC diagnosis (HR = 4.196, p < 0.0005). RAS, BRAF or PIK3CA were not associated with BM. On multivariate cox regression, only presence of lung metastases (HR = 3.534, p < 0.0005) was significantly associated with increased hazard of BM.

Conclusions: The incidence of BM was 8.8 % in our cohort of long surviving patients with mCRC. Having lung metastases at mCRC diagnosis seem to be an independent risk factor for later BM development. Rectal cancer and metastatic metastatic disease were also linked to an increased risk of BM.

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### Table: 583P Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>BM 43 patients</th>
<th>BM 42 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at CRC diagnosis (years)</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>Rectal cancer (%)</td>
<td>153 (35 %)</td>
<td>26 (62 %)</td>
</tr>
<tr>
<td>Metastatic disease (%)</td>
<td>188 (43 %)</td>
<td>28 (67 %)</td>
</tr>
<tr>
<td>Lung metastases (%)</td>
<td>130 (30 %)</td>
<td>26 (62 %)</td>
</tr>
<tr>
<td>RAS Mut (%)</td>
<td>184 (42 %)</td>
<td>20 (48 %)</td>
</tr>
<tr>
<td>BRAF Mut (%)</td>
<td>30 (7 %)</td>
<td>0</td>
</tr>
<tr>
<td>PIK3CA Mut (%)</td>
<td>58 (13 %)</td>
<td>7 (16 %)</td>
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Legal entity responsible for the study: Troels Dreier Christensen and Dorte Lübet Nielsen

Funding: The Danish Cancer Society

Disclosure: All authors have declared no conflicts of interest.

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### 583P Prognostic factors in patients with locally advanced rectal cancer who underwent preoperative chemoradiotherapy: Subclassification of patients with ypStage II cancer according to tumor regression grade

T. Suzuki, S. Sadahiro, G. Saito, K. Okada, A. Tanaka

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**Background:** Preoperative chemoradiotherapy (CRT) is the standard of care for locally advanced rectal cancer. Patients with a marked improvement of outcomes with low risk of local and distant recurrence. Histological response can be evaluated on the basis of T or N downstaging, and tumor regression grade (TRG). Some patients with ypStage II are evaluated to have no downstaging because of the presence of small amounts of residual cancer cells in the T3 layer even if they have a marked reduction in tumor volume and a TRG of 2. We therefore studied whether the combination of ypStage and TRG could be used as a prognostic factor.

**Methods:** We studied 191 patients with cT3/T4, Nx, or cT2, N + , M0 adenocarcinoma of the rectum who underwent surgery after CRT from 2007 to 2015. The total radiation dose was 40 or 45 Gy given in combination with irinotecan as third-line treatment independently of RAS status (positive vs negative), GDS (7 vs 8-10), Spitzer QoL (7 vs 8-10), age (≤ 75 vs >75), sex (male vs female), occupational status (≤ 31 vs >31), Spitzer QoL (7 vs 8-10), and GDS (7 vs 8-10). The primary endpoint based on efficacy and safety was reached in BEV-CT. This analysis presents updated progression-free survival (PFS) and overall survival (OS), including univariate and multivariate analyses. The primary endpoint was progression or death and OS.

**Results:** Recurrence was found in 47 patients (25%). The initial site of recurrence was local in 5 patients (3%), the liver in 16 (8%), and the lung in 19 (10%). The ypStage was 0 in 39 patients (20%), I in 45 (24%), II in 62 (32%), and III in 45 (24%). Downstaging was noted in 44% of the patients. The TRG was 1 in 32 patients (17%), 2 in 49 (26%), 3 in 75 (39%), and 4 in 35 (18%). The median follow-up was 55 months, the 5y DFS was 71%, and the 5y OS was 85%. The 5y DFS according to ypStage was 82% in 0 or I, 56% in II or III cancer, and the 5y OS was 90% and 82%, respectively. Survival rates were significantly higher in ypStage 0 or I cancer than in ypStage II or III cancer (p = 0.0003 and p = 0.0046). The 5y DFS was 83% in patients with ypStage 0 or I or ypStage II cancer with a TRG of 2, as compared with 58% in other patients. The 5y OS was 92% and 79%, respectively. Survival rates were significantly higher in patients with ypStage 0 or 1 or ypStage II cancer with a TRG of 2 (p < 0.0001 and p = 0.0055).

**Conclusions:** Outcomes were good in most patients with ypStage II cancer who had a TRG of 2. Combining the TRG histological response with ypStage may be a better prognostic indicator than ypStage alone.

**Legal entity responsible for the study:** N/A

**Funding:** Tokai University

**Disclosure:** All authors have declared no conflicts of interest.
questionnaire (≥2 vs ≤2), fall in the 6 months previous randomization or one-leg balance, presence of anemia, albumin (≥35 vs ≤35 g/L), creatinine clearance (≥45 vs ≤45 mL/min), CEA (≥20 vs ≤20), CA19.9 (≥2 vs ≤20) and Kôhne criteria (low vs intermediate vs high). Baseline variables significant at 15% in univariate analysis were introduced into a multivariate Cox model.

Results: 102 pts were randomized (51 BEV-CT, 51 CT) and 100 pts were treated: chemotherapy was LV5FU2 in 52 pts (26 BEV-CT, 26 CT) and a doublet regimen in 48 pts (23 BEV-CT, 25 CT) including 23 FOLFOX and 25 FOLFIRI. The median follow-up was 20.4 months. 25 pts BEV-CT and 31 pts CT received 2nd line chemotherapy. Multivariate analysis shows thatSpitzer QoL, albumin and Kôhne criteria were prognostic for OS. Spitzer QoL and Kôhne criteria were also prognostic for PFS.

Conclusions: Spitzer QoL, and Kôhne criteria are prognostic factors for OS and PFS and should be used as stratification factors in future trials in elderly pts. Pts with a prolonged OS were observed in BEV-CT.

Clinical trial identification: NCT01900717

Legal entity responsible for the study: CHU Dijon

Funding: Programme Hospitalier de Recherche Clinique and Roche laboratory

Disclosure: T. Aparicio; Roche/Genentech, Sanofi, Ipsen, Novartis. O. Bouché; Merck Serono, Roche, Teva, Novartis, Lilly, Amgen, Pierre Fabre. E. Francois; Roche Pharma AG, Merck Serono, Roche Pharma AG, Sanofi, Celgene. J. Taeb; Roche Pharma AG. R. Faroux; Merck, Amgen. C. Lacher; Merck Serono, Novartis, Roche Pharma AG, Sanofi. S. Lavau-Denes; Sanofi, AstraZeneca. L. Bedene; Merck Serono, Roche Pharma AG. All other authors have declared no conflicts of interest.

<table>
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<tr>
<td>CT [95% CI]</td>
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<tr>
<td>Median PFS (m)</td>
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<tr>
<td>12 months PFS rate</td>
</tr>
<tr>
<td>Median OS (m)</td>
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<td>36 months OS rate</td>
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</table>

**Conclusions:** Stratification of patients with locally advanced rectal cancer (LARC) treated with preoperative chemoradiation (CHR), according to Valentini’s nomograms (VN) and the Neoadjuvant Rectal Score (NAR), External validation in a single institution.


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Background: Preoperative CHR is the standard of care for LARC. The estimation of risk of locoregional (LR) or systemic recurrence (SR) or death is mainly based upon pathological and clinical features. Valentini et al. (JCO 2011) developed 3 nomograms to predict the 5-year probability of locoregional or distant control as well as overall survival (OS) with patients from 5 European randomized clinical trials. The NAR (Curr Colorectal Cancer Rep 2015) was developed after VN for OS combining the three variables (CT, pT and pN) with the greatest weight in the model. Both VN and NAR had an external validation.

Methods: 158 consecutive patients from a single academic institution were diagnosed of LARC between 1998 and 2011 and treated with CHR followed by total mesorectal excision. Most of them received adjuvant chemotherapy (ACh). The variables used in the nomograms were sex, age, clinical stage, tumor location, radiotherapy dose, chemotherapy, surgical procedure and ypTNM stage. According to the score obtained, the nomograms were sex, age, clinical stage, tumor location, radiotherapy dose, chemotherapy, surgical procedure and ypTNM stage. According to the score obtained, all 3 nomograms were classified according to: poor metabolizers (PM: 5-FU-DR ≤ 22 ng/mL/10^6 cells/min). DNA pyrosequencing was used to detect gene polymorphisms of MTHFR, DPYD and TSER. Toxicities were classified according to CTCAE v 4.0. Statistical analysis was performed with SPSS2 software. Pearson’s Chi square test was used to correlate gene polymorphisms and 5-FU-DR with toxicities.

Results: We analyzed 126 resected CRC patients (91 M, 35 F; median age 65 y, range 36-81 y), receiving adjuvant FOLFOX. 7 patients were PM, 116 NM and 3 UM. Median 5-FU-DR was 1.495 ng/ml/10^6cells/min (range 0.42-2.2). G3-4 toxicities were observed in 22.2% of the cases: 59.3% hematological, 29.6% gastrointestinal, 7.4% neurologic and 3.7% others. A higher G3-4 toxicity incidence was observed in PM

**Table: S38P**

<table>
<thead>
<tr>
<th>CT [95% CI]</th>
<th>BEV + CT [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (m)</td>
<td>7.8 [6.6-10.2]</td>
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<tr>
<td>12 months PFS rate</td>
<td>23.5% [13.0-35.8]</td>
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<tr>
<td>Median OS (m)</td>
<td>19.8 [13.9-23.7]</td>
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<tr>
<td>36 months OS rate</td>
<td>10.1% [5.1-22.9]</td>
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Clinical characteristics of colorectal cancer patients with brain metastases: An "Association des Gastro-Éntérologues Oncovénaux" (AGEO) multicenter study

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Background: Brain metastases (BM) from colorectal cancer (CRC) are rare (1-3%) but their incidence seems to be increasing due to improvement of CRC prognosis. The prognosis of patients with BM from CRC is poor. The objective of this study was to evaluate the clinicopathological criteria of BM with CRC. Methods: This multicenter retrospective study included all patients with BM from CRC between 1995 and 2015. Overall survival was calculated using the Kaplan-Meier method. Results: A total of 135 patients were included. Mean age at diagnosis of CRC was 65.5 years [range 34-87] and 57.8% were men. Primary tumors were located preferentially in the rectum (37.1%) or sigmoid (24.3%). The median interval from CRC diagnosis to BM diagnosis was 34.2 months [95% CI: 28.8-38.7] and the one from the diagnosis of CRC metastases to BM diagnosis 20.7 months [95% CI: 13.2-26.1]. BM were mostly revealed by neurological symptoms (93.3%), predominantly unilateral (36.4%) and supratentorial (74.1%). At BM diagnosis, 71.1% of patients had lung metastases, 48.9% liver metastases and 11.9% had no extra-cerebral metastasis. BM resection was performed in 37.1% of the cases and 76.5% of patients underwent a brain radiotherapy. The mean overall survival from the time of BM diagnosis was 8.7 months [IC95%: 6.7-10.7], respectively 14.8 months [IC95%: 10.8-18.7] in the group of patients who underwent surgical resection versus 4.9 months [IC95%: 3.0-6.8] for the others (p < 0.0001). Overall survival was 12.3 months [IC95%: 9.0-15.7] for patients with unifocal BM versus 4.9 months [IC95%: 3.2-6.6] for patients with multifocal BM (p < 0.0001). Molecular analyses (RAS and BRAF) are ongoing and will be presented at the congress. Among the 34 CRC with available KRAS status, KRAS mutation was observed in 58.8% of the cases. Conclusions: The prognosis of patients with BM from CRC remains poor. Patients with BM from CRC have frequently lung metastases. The time between diagnosis of CRC metastases and BM raises the question of BM screening at 1-2 years of metastatic disease. Early detection of BM from CRC can allow curative-intent aggressive treatment with an expected benefit on survival and quality of life.

Legal entity responsible for the study: Pauline Roussille

Funding: AGEO

Disclosure: All authors have declared no conflicts of interest.

Is the derived neutrophil to lymphocyte ratio (dNLR) an independent prognostic marker in patients with metastatic colorectal cancer (mCRC)? Analysis of the CO.17 and CO.20 studies


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Background: dNLR (neutrophil count /total white cell - neutrophil count) has shown prognostic utility for overall survival (OS) in a number of cancers. The CCTG/AGITG CO.17 and CO.20 studies examined the EGFR inhibitor, cetuximab (C), versus best supportive care, and in combination with the VEGF/FGFR inhibitor brivanib (B) or placebo, respectively, in previously treated patients with mCRC. Here, we examine dNLR in CO.17 and CO.20 for its utility to predict progression free survival (PFS), response rate (RR) and OS.

Methods: Association between dNLR status and PFS, OS and RR was analysed using multivariate regression models adjusting for baseline (BL) disease and patient (pt) characteristics. Interaction between treatment and dNLR status was studied by including an additional interaction term. Results: CO.17 recruited 572 pts; 570 pts had available BL dNLR data. CO.20 recruited 750 pts; 718 had BL data available. In both, pts with high BL dNLR (≥2) were significantly more likely to have poorer ECOG status, received more lines of therapy, alkaline phosphatase and lactate dehydrogenase levels, 2 grade 1 anemia, acrines, presented with lung metastases, have ≥2 sites of metastases. Multivariate analyses results are summarised in Table 1. Both studies showed pts with high dNLR had significantly shorter OS. Significant association of dNLR status with PFS was only found in CO.20 but no significant association with RR was found in either study. Significant association was found with OS in all four treatment groups, but for PFS, in C+ B arm of CO.20 only. In both studies, no significant interaction was found between dNLR status and treatment for either OS or PFS.

Results: CO.17 recruited 572 pts; 570 pts had available BL dNLR data. CO.20 recruited 750 pts; 718 had BL data available. In both, pts with high BL dNLR (≥2) were significantly more likely to have poorer ECOG status, received more lines of therapy, alkaline phosphatase and lactate dehydrogenase levels, 2 grade 1 anemia, acrines, presented with lung metastases, have ≥2 sites of metastases. Multivariate analyses results are summarised in Table 1. Both studies showed pts with high dNLR had significantly shorter OS. Significant association of dNLR status with PFS was only found in CO.20 but no significant association with RR was found in either study. Significant association was found with OS in all four treatment groups, but for PFS, in C+ B arm of CO.20 only. In both studies, no significant interaction was found between dNLR status and treatment for either OS or PFS.

Table: S8BP Multivariate analysis of dNLR in CO.17 and CO.20

<table>
<thead>
<tr>
<th></th>
<th>CO.17</th>
<th>CO.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RR</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions: The dNLR has independent prognostic utility for OS in previously treated patients with mCRC. This provides a simple, inexpensive prognostic biomarker for heavily pre-treated mCRC patients and should be considered as a stratification factor in future clinical trials.

Clinical trial identification: Clinicaltrials.gov CO.20: NCT00640471 CO.17: NCT00790686

Legal entity responsible for the study: Canadian Cancer Trials Group Australian Gastro-Intestinal Trials Group


References:

Disease. Early detection of BM from CRC can allow curative-intent aggressive treatment with an expected benefit on survival and quality of life. All other authors have declared no conflicts of interest.
Background: NLR (ratio of absolute neutrophil and lymphocyte counts) has shown prognostic utility for OS in a number of cancer types. The AGITG MAX study examined capcitabine (C) with C + bevacizumab (B) and C + B + mitomycin C (M) in first-line treatment of mCRC. CB demonstrated superiority over C for PFS and was comparable to CBM. We examine NLR in the MAX study to assess its utility for prediction of treatment effect, PFS and OS.

Methods: NLR estimates were obtained using the method of Kaplan-Meier and hazard ratios obtained using proportional hazards models. Analysis included adjusting for baseline (BL) disease and patient (pt) characteristics and investigating potential interaction effects between NLR status and significant BL predictors of outcome.

Results: MAX study recruited 471 pts; relevant BL haematological data was available for 403 pts (86%). At BL, 24% of pts had high NLR (≥5). High NLR correlated with rectal primary (p = 0.007), higher ECOG status (p < 0.001), more prior therapy (i.e. prior adjuvant/neoadjuvant) (p = 0.01), more sites of metastases (p = 0.006). Results of univariate analysis summarised in Table 1. On univariate analysis, pts with high NLR (≥5) had 87.2 months, the group MPV > 8.3 had 59.7 months, the group MPV > 8.3 had 87.2 months; the group MPV > 8.3 had 12-month follow-up period; the patients had non-metastatic cancer at the time of diagnosis. In order to find out NLR, PLR, and MPV cut-off values, ROC curve analysis was used. Figure 1. ROC Curves of NLR, PLR and MPV for respective patients MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio, PLR, platelet/lymphocyte ratio, ROC (receiver-operating characteristic.)

Results: Findings: Patients were categorized into two groups according to positive relapse and negative relapse: 89 patients (26.5%) experienced a relapse in the follow-up period. The group NLR ≤ 3.39 had 55.5 months of disease-free survival (p < 0.001) while the group NLR > 3.39 had 82.8 months (p < 0.001). The group PLR ≤ 183 had 57.8 months, the group PLR > 183 had 78.7 months (p = 0.016); the group MPV ≤ 8.3 had 59.7 months, the group MPV > 8.3 had 87.2 months; the group MPV > 8.3 had 97.2 months and the group MPV < 8.3 had 59.7 months (p = 0.057).

Table 588P Univariate analysis of baseline NLR in MAX study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Factor</th>
<th>Median (mo)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
<th>Univariate</th>
<th>HR (95% CI)</th>
<th>p-value</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>NLR &lt; 5</td>
<td>7.5 (6.9-8.5)</td>
<td>1.4 (1.1-1.8)</td>
<td>0.006</td>
<td>0.004</td>
<td>1.4 (1.1-1.8)</td>
<td>0.006</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>NLR ≥ 5</td>
<td>5.9 (4.7-7.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS</td>
<td>NLR &lt; 5</td>
<td>19.8 (17.3-21.4)</td>
<td>1.9 (1.4-2.4)</td>
<td>0.001</td>
<td>0.001</td>
<td>1.8 (1.3-2.3)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>NLR ≥ 5</td>
<td>12.1 (8.4-14.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* after adjustment for other significant prognostic factors

Conclusions: NLR provides independent prognostic information for patients with mCRC receiving first-line treatment in the MAX study, for both PFS and OS. This should become a standard stratification indication for future randomised controlled trials.

Clinical trial identification: ANZ.Clinical Trial Registry ACTRN12605000025639

Legal entity responsible for the study: Australian Gastro-Intestinal Trials Group

Funding: Lead sponsor: Australian Gastro-Intestinal Trials Group Funded: Roche


Table 590P Clinical characteristics of the patients with colorectal cancer

<table>
<thead>
<tr>
<th>Characteristics of the patients</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean (range)</td>
<td>62.2 ± 11.8 (33-86)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>211 (62.8)</td>
</tr>
<tr>
<td>Female</td>
<td>125 (37.2)</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>27 (8.0)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160 (47.6)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>149 (44.4)</td>
</tr>
<tr>
<td>Degree of differentiation</td>
<td></td>
</tr>
<tr>
<td>Well-differentiated</td>
<td>85 (25.3)</td>
</tr>
<tr>
<td>Moderately-differentated</td>
<td>207 (61.6)</td>
</tr>
<tr>
<td>Poorly-differentiated</td>
<td>44 (13.1)</td>
</tr>
<tr>
<td>Disease status at last follow-up</td>
<td></td>
</tr>
<tr>
<td>Evidence of disease (ED)</td>
<td>89 (26.4)</td>
</tr>
<tr>
<td>No evidence of disease (NED)</td>
<td>247 (73.6)</td>
</tr>
<tr>
<td>Tumor localization</td>
<td></td>
</tr>
<tr>
<td>rectal</td>
<td>66 (19.6)</td>
</tr>
<tr>
<td>colon</td>
<td>270 (80.3)</td>
</tr>
</tbody>
</table>

Conclusions: Our study demonstrated that NLR, PLR and MPV levels can actually be relied on as a prognostic factor in patients with CRC. MPV, NLR and PLR values displayed by recently diagnosed patients with CRC may be a reflection of an increased cytokine level and thereby change depending on it.

Legal entity responsible for the study: N/A

Funding: Izmir Oncology Group (IZOG) Study

Disclosure: All authors have declared no conflicts of interest.

591P

Reduction of blood total lymphocyte count after neoadjuvant treatment is correlated with good tumor regression—results from a prospective randomized control trial

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Medical Oncology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Blood total lymphocyte count (TLC) before treatment had been reported to be play an important role in tumor immune response. The study aimed to evaluate whether the change of TLC was correlate with tumor regression grade (TRG) after neoadjuvant treatment in locally advanced rectal cancer patients.
Methods: TLC before and after neoadjuvant therapy were collected from available 307 patients in FOWARC study. The ratio of TLC reduction after neoadjuvant therapy was calculated. TRG 0-1 was defined as good responder. The correlation between TRG and the ratio of lymphocyte reduction was evaluated.

Results: Of the 307 patients, 153 were good responder (TRG 0-1), and 154 had poor response (TRG 2-3). The base line TLC before neoadjuvant therapy have no significant difference (p = 0.296) between good and poor responders. After neoadjuvant therapy, 85% of patients experienced TLC reduction. TLC after neoadjuvant treatment was lower in good response group than that of poor response group, with a median TLC of 1.08 and 1.29, respectively (p = 0.011). In the group with neoadjuvant chemotherapy alone. TLC reduction was more obvious in good responder. The median ratio of TLC reduction after neoadjuvant were 39.41% and 33.33% in good and poor responder groups, respectively (p = 0.037).

Conclusions: TLC reduction is more apparent in patients with good response after neoadjuvant treatment. The consumption of lymphocytes might indicate the immune response inside tumors after neoadjuvant treatment, which could be a predictor of sensitivity to preoperative therapy.

Legal entity responsible for the study: Yanhong Deng

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

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**Table S1P**

<table>
<thead>
<tr>
<th>Item</th>
<th>Good response group</th>
<th>Poor response group</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>TRG1</td>
<td>TRG2</td>
</tr>
<tr>
<td>Rate of TLC reduction of all 307 patients</td>
<td>36.00% ± 3.56%</td>
<td>36.00% ± 2.99%</td>
</tr>
<tr>
<td>Rate of TLC reduction in chemotherapy group TLC before neoadjuvant</td>
<td>27.0% ± 4.19%</td>
<td>9.70% ± 5.12%</td>
</tr>
<tr>
<td>TLC after neoadjuvant</td>
<td>2.00 ± 0.04</td>
<td>1.20 ± 0.04</td>
</tr>
</tbody>
</table>

**Is neutropenia a prognostic or a predictive factor for second metastatic colorectal cancer (mCRC) patients? (Pts)**

**Exploratory analysis from RAISE, a randomized, double-blind, phase III study of ramucirumab (RAM) + FOLFIRI vs placebo (PBO) + FOLFIRI**


Background: Neutropenia may be a prognostic or predictive factor for pts with mCRC. This is the first propensity-score adjusted population-based investigation of outcomes in patients with mCRC in the RAISE study (Simkens et al. Lancet 2015) in which mCRC patients with stable disease or better after 6 cycles capecitabine + oxaliplatin + bevacizumab (CAPOX-B) were included in the analysis if they developed any-grade neutropenia after the initiation of study treatment. Overall survival (OS) was analyzed using the Kaplan-Meier method.

Results: In the RAISE study, pts were randomized 1:1 to receive 8 mg/kg IV RAM + FOLFIRI or PBO + FOLFIRI every 2 weeks. Pts from both treatment arms were included in the analysis if they developed any-grade neutropenia after the initiation of study treatment. Overall survival (OS) was analyzed using the Kaplan-Meier method.

Conclusions: Neutropenia may be a prognostic or predictive factor for pts with mCRC. These results suggest that the treatment effect of RAM in neutropenic pts with mCRC is unlikely to be compromised despite lower chemotherapy dose intensity. Additional analyses are underway to elucidate the meaning and the biological mechanism of the effect of RAM in neutropenic pts.

Clinical trial identification: ClinicalTrials.gov NCT01183780

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company

Disclosure: T.-E. Ciuleanu: Consultant/Advisory board Eli Lilly, Roche, Merck, Amgen. G. Bodoky: I was attending an advisory board of Lilly. NO financial interest in products or processes involved in this research. This includes stock ownership, corporate-sponsored research, or other substantive relationships. R. Garcia-Carbonero: Scientific advise to Roche, Merck, Sanofi, Amgen, Bayer, Lilly. P. Garcia-Alfonso: Advisory role: Roche, Merck, Amgen, Bayer, Sanofi. Celgene. Lilly. Speaker: Roche, Merck, Amgen, Lilly. E. Van Cutsem: Research Grant from Lilly Consultant. Lilly. D. Mytelka, O. Lipkovitch, D. Ferré, A. Sashegyi, F. Nasrallah: Employee and shareholder of Eli Lilly and Company. J. Tabernero: Consultant/Advisory role: Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Merck Serono, Novartis, Roche, Sanofi, Symphogen, Takeda, Taiho. All other authors have declared no conflicts of interest.

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**Table S1P**

<table>
<thead>
<tr>
<th>Prognostic value of signet ring cell histology for survival in stage I and II colon cancer patients: a population-based, propensity score matched analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>U. Güder1, T. Cenzer2, B. Schniedt3, R. Warschnow</td>
</tr>
<tr>
<td>1Department of Oncology/Hematology, Kantonsspital St. Gallen, St. Gallen, Switzerland, 2Internal Medicine, Kantonsspital St. Gallen, St. Gallen, Switzerland, 3Surgery, Kantonsspital St. Gallen, St. Gallen, Switzerland</td>
</tr>
</tbody>
</table>

Background: Previous retrospective research associated signet ring cell histology with poor oncologic outcomes in colon cancer patients. However, potential bias cannot be ruled out in previous studies. This is the first propensity-score-based investigation assessing the prognostic impact of signet ring histology on overall and cancer-specific survival in patients with stage I and II colon cancer.

Methods: Stage I and II colon cancer patients undergoing surgery between 2004 and 2013 were identified in the Surveillance, Epidemiology, and End Results (SEER) database. Overall survival (OS) and cancer-specific survival (CSS) were assessed using risk-adjusted Cox proportional hazards regression models and propensity score methods.

Results: Overall, 75,134 stage I-II colon cancer patients were included, of which 380 (0.5%) with signet ring cell histology. In unadjusted analyses, the 5-year OS and CSS in patients with signet ring cell histology was 64.7% (95% confidence interval (CI): 59.3-70.6) and 84.1% (95% CI: 79.9-88.6) compared with 73.9% (95% CI: 73.6-74.3%) and 88.6% (95% CI: 88.3-88.9), respectively, in patients with non-signet ring adenocarcinoma (P = 0.003 and P = 0.026). The survival disadvantage disappeared in risk-adjusted Cox proportional hazards regression analysis (OS: hazard ratio (HR) = 0.96, 95% CI: 0.80-1.15; P = 0.647; CSS: HR = 0.89, 95% CI: 0.76-1.11; P = 0.357 and CSS: HR = 0.86, 95% CI: 0.63-1.16; P = 0.315).

Conclusions: This is the first propensity-score-based adjusted population-based investigation on exclusively stage I and II colon cancer patients providing compelling evidence that signet ring cell histology does not negatively impact survival. Therefore, standard treatment strategies can be applied in these patients.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

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**Table S1P**

<table>
<thead>
<tr>
<th>Evolution of skeletal muscle mass (SMM) during palliative systemic treatment in metastatic colorectal cancer (mCRC) patients participating in the randomized phase 3 CAIRO3 study</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.A. Kuijf1, P.H.M. Peeters2, B. Borrestijn2, M. Jourdan3, H.J. Kuijf4, C. Punt5, M. Hoogstraten1, A.M. Maas3</td>
</tr>
<tr>
<td>1Medical Oncology, University Medical Center Utrecht, Utrecht, Netherlands, 2Public Health, Imperial College London-South Kensington Campus, London, UK, 3Oncology, Nutricia Research, Utrecht, Netherlands, 4Image Science Institute, University Medical Center Utrecht, Netherlands, 5Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, 6Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands</td>
</tr>
</tbody>
</table>

Background: Observational studies suggest that low SMM is associated with chemotherapy-related toxicity and poor survival in mCRC patients. Little is known about patterns of SMM during palliative systemic treatment. Here we use data of the CAIRO3 study (Simkens et al. Lancet 2015) in which mCRC patients with stable disease or better after 6 cycles capecitabine + oxaliplatin + bevacizumab (CAPOX-B)
were randomized between maintenance treatment with capecitabine + bevacizumab (CAP-B, M) and observation (O). In both groups CAPOX-B or other treatment was reintroduced upon disease progression after second line chemotherapy. In this study, our first aim was to assess the relation between different endpoints of patients with mCRC treated with 1st-line bevacizumab-based regimen. Although studies have shown prognostic capacity for SMM, the effect of subsequent changes in SMM is unknown and may be clues for new future therapeutic interventions.

Conclusion: Our data shows that muscle loss in mCRC patients during palliative chemotherapy treatment varies with treatment regimen. Although studies have shown prognostic capacity for SMM, the effect of subsequent changes in SMM is unknown and may be clues for new future therapeutic interventions.

Clinical trial identification: ClinicalTrials.gov NCT00442637

Legal entity responsible for the study: Sophie Kurk

Funding: University Medical Center Utrecht

Disclosure: B. Dorresteijn, M. Jourdan: Employee of Nutricia Research. C. Punt: Advisory role: Roche, Amgen, Bayer, Nordic Pharma, Merck-Serono. M. Koopman: Advisory role: Amgen, Roche, Bayer, Merck. Research funding: Roche, Merck, Bayer. All other authors have declared no conflicts of interest.

Correlation between alternative endpoints and overall survival in metastatic colorectal cancer patients eligible to a maintenance strategy

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1OncoMedecale, Centre Oscar Lambret, Lille, France, 2Unité de Méthodologie et QuaLité de vie en cancérologie (EQUIPE), CHU de Besançon, Besançon, France, 3Département of Medicine DITEP, Institut Gustave Roussy, Villejuif, France, 4Oncologie médicale, Hopital Saint Vincent, Lille, France, 5Dépt de Cancérologie Digestive, Centre Oscar Lambret, Lille, France

Background: In this study, our first aim was to assess the relation between different intermediate criteria and overall survival (OS) in patients treated for a metastatic colorectal cancer (mCRC) receiving a first-line chemotherapy associated with bevacizumab.

Methods: We collected retrospective data from patients with mCRC treated with 1st-line chemotherapy (generally FOLFIRI-FOLFOX regimen) plus bevacizumab between January 2006 and December 2012. We assessed at the following timepoints: OS, progression free survival (PFS), duration of disease control (DDC), the sum of the periods in which the disease did not progress, and the time to failure of strategy (TFS), respectively. Prentice criteria were verified for both TFS and DDC, respectively. Linear correlation and linear regression models were used to study relations between OS and TFS, and OS and DDC, respectively. Prentice criteria for surrogacy were investigated.

Results: We included 216 patients from 6 centers. 91 (42%) patients received a maintenance strategy. With a median follow-up of 57.4 (34.2-94.0) months, OS median was 24.5 (21.3-29.7) months, median PFS was 8.9 (8.4-9.7) months, median DDC was 11.1 (10.0-13.0) months. Pearson coefficient (coefficient) was 0.79 (CI 95% 0.73-0.83) and determination coef was 0.62, suggesting of a satisfactory correlation between OS and DDC. Similarly, the correlation between OS and TFS was rather satisfactory with a Pearson coefficient at 0.79 (CI 95% 0.73-0.84) and a determination coeff at 0.63. Linear regressions analysis showed a significant association between OS and DDC, both OS and TFS, respectively. These relationships can be modeled by the formulas: cube root (SO) = 0.9547 + 0.6286 cubic root (DDC) and cubic root (SO) = 0.965 + 0.8186 cubic root (TFS). Considering resection of metastases as the treatment, Prentice criteria were verified for both TFS and DDC.

Conclusions: DDC and TFS were correlated to OS and Prentice criteria were validated for both endpoints. This makes them relevant as intermediate criteria, in the setting of patients mCRC treated with 1st-line bevacizumab-based regimen. Legal entity responsible for the study: CHRU de Lille

Funding: CHRU de Lille

Disclosure: All authors have declared no conflicts of interest.
**APOLLO study: a phase I/II study for the safety and efficacy of panitumumab in combination with TAS-102 with patients with RAS wild-type metastatic colorectal cancer refractory to standard chemotherapy**


Department of Gastroenterology, Cancer Institute Hospital of JFCR, Tokyo, Japan

Cancer Center, Hokkaido University Hospital, Sapporo, Japan

Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Gastroenterology & Gastrointestinal Oncology, National Cancer Center Hospital East, Kashihara, Japan

Gastrointestinal Oncology and Endoscopy, Shizuoka Cancer Center, Shizuoka, Japan

Medical Affairs, Takeda Pharmaceutical Company Ltd., Tokyo, Japan

Department of Biostatistics, School of Public Health, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

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**Background:** Anti-EGFR antibodies (Panitumumab (Pmb)/Cetuximab (Cmb)) have established efficacy and manageable safety profiles either in monotherapy or in combination with chemotherapy for the treatment of metastatic colorectal cancer (mCRC) patients. In recent global phase III RECOURe study, TAS-102 significantly improved OS and PFS over placebo for mCRC pts refractory to standard chemotherapy. In preclinical models, the combination of Pmb with TAS-102 demonstrated enhanced activities compared with either drug alone. This phase I/II study is designed to investigate the safety and efficacy of Pmb combination with TAS-102 for pts with RAS (KRAS/NRAS) wild-type mCRC refractory to standard chemotherapy.

**Trial design:** Eligible pts are aged 20-74 y, ECOG performance status 0-1 with histologically/cytologically confirmed RAS wild-type mCRC, and refractory or intolerant to fluoropyrimidines, irinotecan, oxaliplatin, and anti-angiogenesis therapy and had neither prior anti-EGFR antibody nor regorafenib treatment. Phase I part is designed to determine recommended phase II dose (RPD) in the dose de-escalation design of Pmb (6 mg/kg) every 2 weeks combination with TAS-102 (35 mg/m² BID on days 1–5 and 8–12, every 4 weeks). The primary objectives are to evaluate the incidence proportion of DLTs (phase I) and to evaluate the investigator assessed PFS rate at 6 months (phase II). In order to evaluate the effect of TAS-102 in addition to Pmb monotherapy, an exact binomial test with a nominal one-sided 5% significance level was predicted to have at least 80% power to detect the difference between the null hypothesis proportion of 29% PFS rate and the alternative proportion of 48% PFS rate.

**Disclosure:** K. Yamaguchi: Honoraria (speaker’s bureau): Takeda, Tahto, Merck, Chugai, Eli-Lilly. Research funding for clinical trials from Takeda, Tahto, Merck, chugai, Eli-Lilly. K. Yamazaki: Honoraria (speaker’s bureau) and Research funding from Novartis, Pfizer, Bayer, yakult, Daichi-Sankyo, Kyoya-Kirin, Chugai, Merck-Serono, BMS, Taheo, Tahto, Eli-Lilly. E. Okl has received Honoraria (lecture fee) from Takeda, Tahto, T. Yoshino: Research funding for clinical trials from GlaxoSmithKline, Boehringer Ingelheim. K. Yamazaki: Honoraria (lecture and/or manuscript fee) from Bayer, yakult, Daichi-Sankyo, Chugai, Merck-Serono, BMS, Taheo, Takeda. Research funding from BMS, K. Shibuya: Employee of Takeda. K. Otani: Honoraria (lecture and/or manuscript fee) from Takeda, BMS, Ono, Chugai. T. Kato: Honoraria (lecture fee) from Bayer, yakult, Chugai, Merck-Serono, Takeda.

**Clinical trial identification:** ClinicalTrials.gov NCT026131221

**Legal entity responsible for the study:** MHLW, Japan

**Funding:** Takeda pharmaceutical Co., ltd.

**Disclosure:** K. Yamaguchi: Honoraria (speaker’s bureau): Takeda, Tahto, Merck, Chugai, Eli-Lilly. Research funding for clinical trials from Takeda, Tahto, Merck, chugai, Eli-lilly. K. Yamazaki: Honoraria (speaker’s bureau) and Research funding from Novartis, Pfizer, Bayer, yakult, Daichi-Sankyo, Kyoya-Kirin, Chugai, Merck-Serono, BMS, Taheo, Tahto, Eli-Lilly. E. Okl has received Honoraria (lecture fee) from Takeda, Tahto, T. Yoshino: Research funding for clinical trials from GlaxoSmithKline, Boehringer Ingelheim. K. Yamazaki: Honoraria (lecture and/or manuscript fee) from Bayer, yakult, Daichi-Sankyo, Kyoya-Kirin, Chugai, Merck-Serono, BMS, Taheo, Takeda. Research funding from BMS, K. Shibuya: Employee of Takeda. K. Otani: Honoraria (lecture and/or manuscript fee) from Takeda, BMS, Ono, Chugai. T. Kato: Honoraria (lecture fee) from Bayer, yakult, Chugai, Merck-Serono, Takeda.

**A randomized phase III trial of capcitabine with or without irinotecan driven by UGT1A1 in neoadjuvant chemoradiation of locally advanced rectal cancer (CinClare)**


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**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 25%. ABIO filetype trial, a multicentre UK-based phase III trial, will complete recruitment in autumn 2016. However, all patients in case group were prescribed with weekly irinotecan dose of 60mg/m² for four times, regardless of the genotype of UGT1A1, which has been regarded in favor of predicting toxicities. In our previous phase I trial, the weekly dose of irinotecan was escalated to 65mg/m² for two times, guided by UGT1A1*28 6/6 and 6/7 genotypes in neoadjuvant chemoradiation. Therefore, this phase III trial was designed to confirm the potential improvement in outcomes seen with the addition of irinotecan to CRT.

**Trial design:** Eligible patients are randomly allocated to either radiotherapy 50 Gy with concurrent capcitabine, followed by a cycle of capcitabine and oxaliplatin two weeks after the end of CRT (Control arm) or radiotherapy 50 Gy with concurrent capcitabine and irinotecan, followed by a cycle of capcitabine and irinotecan (Case arm). Capcitabine is prescribed with 825mg/m² twice daily from first day of radiotherapy and given 5 days per week during radiotherapy in control group. In the other group, capcitabine dose is 625mg/m² twice daily and additional weekly irinotecan dose is 80mg/m² or 65mg/m² guided by UGT1A1*28 6/6 and 6/7 genotypes (total of five times). Stratification was performed by center, UGT1A1*28 genotype (6/6, 6/7, T stage (cT3, cT4), and distance from anal verge (<= 5cm, >5cm). Surgery is performed 6–7 weeks after the end of CRT, then, five cycles of XELOX are recommended during the course of adjuvant chemotherapy. The primary end point is pCR. The hypothesis is to increase pCR 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, progress-free survival and overall survival.

**Clinical trial identification:** NCT02605265, released on December 24, 2015

**Legal entity responsible for the study:** Fudan University Shanghai Cancer Center

**Funding:** Fudan University Shanghai Cancer Center

**Disclosure:** All authors have declared no conflicts of interest.
Background: More than half of the patients diagnosed with mCRC are elderly (>70 years). Older patients comprise a heterogeneous group, they are underrepresented in clinical trials, and knowledge about the best treatment strategy in patients who are not candidates for standard full-dose combination therapy is sparse and it is uncertain whether full dose or reduced dose chemotherapy is the optimal strategy. The oral prodrug S-1 (Teyuse®) is well tolerated as monotherapy and in combinations and could be an ideal drug for older patients (Winther et al. Acta Oncol 2015), but more data to predict toxicity and efficacy is needed. The NORDiC09 study will add knowledge on how to select and tailor the optimal treatment strategy for older mCRC patient who are not candidates for standard combination therapy.

Trial design: NORDiC09 is a randomized phase II trial exploring treatment of older mCRC patients (≥70 years) who are not candidates to full-dose combination therapy, by comparing full dose monotherapy (S-1 30 mg/m² twice daily days 1-14 every 3 weeks or 180-240 mg/m² iv day 1 every 2 weeks) with reduced dose (80%) combination therapy regimen (S-1 20 mg/m² days 1-14 + oxaliplatin 100 mg/m² iv day 1 every 3 weeks or 180-240 mg/m² iv day 1 every 2 weeks) with reduced dose (80%) combination therapy regimen (S-1 20 mg/m² days 1-14 + oxaliplatin 100 mg/m² iv day 1 every 3 weeks, followed by second line irinotecan 250-350 mg/m² iv day 1 every 3 weeks or 180-240 mg/m² iv day 1 every 2 weeks) with reduced dose (80%) combination therapy regimen (S-1 20 mg/m² days 1-14 + oxaliplatin 180 mg/m² iv day 1 every 3 week). Bevacizumab (7.5 mg/kg) may be added at the discretion of the treating clinician. Grafting screening tools (G-8, VES-13, Timed-Up-and-Go, Grip strength), Charlson Comorbidity Index and Quality of Life (EORTC QLQ-C30) will be evaluated at baseline. Blood samples and tumor tissue will be collected to investigate predictive value. Enrollment was initiated in March 2015, and 52 patients are currently included. Primary endpoint is progression-free survival and secondary endpoints are time-to-failure of strategy, overall survival, response rate, toxicity, and correlations between biomarkers, pre-treatment characteristics and geriatric assessments.

Clinical trial identification: EudraCT 2014-008394-39

Legal entity responsible for the study: The Clinical Research Unit, Department of Oncology, Odense University Hospital

Funding: Taiho.

Disclosure: P. Østerlund: Amgen, Bayer, Baxalta, Celgene, Eli Lilly, Merck, Nordic Drugs, Prime Oncology, Roche, Sanofi, P. Pfeiffer: Research grant: Taiho. All other authors have declared no conflicts of interest.

Re-RAD-I external beam radiotherapy for pelvic recurrences in rectal cancer patients previously treated with radiotherapy

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Background: Multimodal treatment of rectal cancer has improved outcome, but some patients still experience local recurrence, which is a major therapeutic challenge after previous radiotherapy (RT). Re-irradiation may improve the rate of radical surgery (R0), as reported in previous studies, where hyperfractionated chemo-RT resulted in 35% R0 rate. Surgery, RT techniques, and imaging have improved recent years, allowing for increased treatment precision with less morbidity. This study investigates re-irradiation of patients with local recurrence in a phase II clinical, imaging and translational study.

Trial design: A prospective multicenter phase II, open label, non-randomised study. Therapy: External beam RT of 40.8 Gy / 1.2 F BD by intensity-modulated RT + CBCT guidance, concomitant capecitabine 825 mg/m² bid all RT days, and surgery 8 weeks post RT. The primary endpoint is R0 rate. Secondary outcomes: Recurrence-free disease and overall survival, acute and late toxicity, patient reported outcomes, translational research, imaging studies for future adaptive RT, mapping of recurrences according to previous RT, and simulation studies of other RT modalities (proton therapy). Main inclusion criteria: Locally recurrent rectal cancer, previous RT and surgery, potentially resectable tumor, age ≥18 years, adequate organ function, acceptable bowel and bladder function, acceptance for translational research. Main exclusion criteria: Central small recurrences deemed resectable, non-resectable distant metastases, medical comorbidities precluding radical surgery, previous RT <12 months prior to recurrence, inability for MRI or PET-CT. Statistics: Simon's two-stage design, with expected R0 of 30% by ITT and expected R0 increase to 45% at ≥0.05, 1 = 0.4. Total sample size is 65 patients. Centers in Denmark and Norway are currently recruiting.

Legal entity responsible for the study: Aarhus University Hospital

Funding: No external funding, it is an academic study. Clinical data collection and treatment related costs will be covered by the local clinical trial unit/ department. Financial support for the sub-studies for translational research, imaging studies and treatment plan simulations will be funded independently, by external funding.

Disclosure: All authors have declared no conflicts of interest.
Background: Aflibercept has already been used in combination with FOLFIRI in the VELOUR trial (1). The aflibercept-LV5FU2 combination can be useful and well tolerated in patients (pts) with never resectable/non symptomatic metastatic colorectal cancer, for whom 5-FU monotherapy can be suggested to delay the toxicities of combined chemotherapy regimens, then eligible for sequential treatment with first-line 5-FU monotherapy. Within this context, it is possible for aflibercept to provide a survival benefit. VELOUR trial did not indicate that toxicity would have a major effect on quality of life, and increase the hoped of prolongation of progression-free survival as the arm with aflibercept. A previous pharmacogenetic analysis of the FFCD 2000-05 phase III trial (2) showed a prognostic and predictive effect of the thymidine synthase (TS)-5UTR polymorphism for response and PFS. The 5-FU monotherapy efficacy was increased in TS 5′R/3′R vs 2R2R-2R3R (2). Stratification in this criterion will confirm or not the prognostic or predictive value of these polymorphisms if linked to the 5-FU efficacy.

Trial design: The major eligibility criteria are: age ≥ 65, performance status ≤ 2, central genotyping of TS in blood DNA. Treatment is administered every 41 days with simplified LV5FU2 regimen, preceded or not by perfusion of 4 mg/kg aflibercept. The treatment will be stopped in case of progression (evaluation each 8 weeks) or toxicities. Eligibility criteria are: TS 5UTR polymorphism, metastatic status. Randomized phase II study of maintenance treatment with mFOLFOX6 plus panitumumab in patients with RAS WT colorectal cancer, for whom 5-FU monotherapy can be suggested to delay the toxicities of combined chemotherapy regimens, then eligible for sequential treatment with first-line 5-FU monotherapy. According to PIK3CA mutational status, BRAF mutational status and EGFR gene copy number, patients are divided into 2 prognostic groups on the basis of their molecular profile: favourable and unfavourable (respectively high and low probability for improved RR). Combination chemotherapy plus anti-EGFR (epidermal growth factor receptor) antibody is approved for first-line therapy in metastatic colorectal cancer in patients with RAS wild type tumors. The combination of FOLFOX with panitumab has led to significantly better outcome when compared to chemotherapy alone. The cumulative oxaliplatin toxicity resulting in dose limiting toxicity has led to the development of maintenance strategies. For FOLFOX plus bevacizumab treated patients a maintenance concept with 5-FU plus bevacizumab has been established by multiple clinical trials. For the use of FOLFOX plus panitumumab, no clear maintenance concept has been defined. The Panamila study is evaluating the concept of limiting the application of chemotherapy agents while continuing with a maintenance treatment including an anti-EGFR antibody. As the EGFR antibody panitumumab is approved for first-line therapy in metastatic colorectal cancer in RAS wild type patients, this study aims to investigate whether addition of a target agent, i.e., panitumumab, to a standard maintenance backbone (5-fluorouracil plus leucovorin) can add/ maintain clinical benefit.

Trial design: Primary Objectives: Efficacy of panitumumab plus 5-FU/FA as maintenance after 12 weeks with mFOLFOX6 plus panitumumab in the first-line treatment of RAS wild type metastatic colorectal cancer patients compared to 5-FU/FA maintenance alone in terms of progression-free survival (superiority design in favor of the combination arm). Secondary Objectives: Time from randomization until failure of treatment strategy (death/progression) Progression-free survival of re-induction Objective response after induction and during maintenance and re-induction Overall survival Safety and skin related Quality of life Sample size Approx. 380 patients will be enrolled. 252 patients should be accrued for randomisation to reach the required number of 218 events (PD or death after treatment with maintenance).

Clinical trial identification: NCT01919873

Legal entity responsible for the study: AIO Studien gGmbH
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Background: The Short Course Oncology Therapy (SCOT) study of adjuvant chemotherapy in colorectal cancer aims to ascertain whether 3 months of treatment is as efficacious as 6 months. The study is designed to assess clinical, quality of life and cost-effectiveness outcomes. However, the unique patient material in the SCOT study could help answer questions in the following translational research areas: Molecular tumour characteristics with prognostic significance in colorectal cancer. Molecular characteristics with predictive significance regarding treatment efficacy and toxicities of 5-FU and oxaliplatin adjuvant treatment in colorectal cancer. Identification of circulating prognostic markers that could be used in personalized follow-up after adjuvant treatment. Identification of genes that could be useful as targets for personalized adjuvant chemotherapy in high-risk patients.

Trial design: SCOT recruited patients from 2008 to 2013. 6144 patients were randomised at 243 sites in 6 countries. For TransSCOT, all patients that have consented to participation in SCOT are asked for further blood samples and permission to access tumour specimen. TransSCOT is currently recruiting patients that have consented to participation in SCOT are asked for further blood samples and permission to access tumour specimen. TransSCOT is currently recruiting patients that have consented to participate in SCOT and biomarker analyses. As of May 11, 2016, study recruitment process is active.

Clinical trial identification: NCT00749450

Legal entity responsible for the study: Department of Oncology, Næstved Hospital, Næstved, Denmark

Funding: Zealand Healthcare Region Foundation for Health Science Research

Disclosure: All authors have declared no conflicts of interest.
Is centralization needed for esophageo-gastric cancer patients with low operative risk? a nationwide study

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Background: Centralization has been shown to improve POM in esophageal and, to a lesser extent, gastric cancer surgery; however, the benefit of centralization for patients with low operative risk is questionable. The aim of the study was to investigate the impact of center volume on postoperative mortality (POM) according to patient condition.

Methods: All consecutive patients who underwent esophageo-gastric cancer surgery between 2010 and 2012 in France were included (n = 11,196). The 30-day POM was compared in terms of the center volume (low: <20 cases per year, intermediate:20-39, high:40-59 and very high ≥60) and stratified according to the Charlson score (0, 1-2, 2-3). The consistency of the esophageal (n = 3286) and gastric (n = 7910) subgroups and variations between 30- and 90-day POM were analyzed.

Results: Low-volume centers treated 64.2% of patients. A linear decrease in 30-day and very high-volume centers, respectively (P < 0.001). Comparing low- and very high-volume centers, 30-day POM was 4.0% vs. 1.1% for Charlson (P < 0.001), 7.5% vs. 3.4% for Charlson1-2 (P < 0.001) and 14.7% vs. 3.7% for Charlson ≥ 3 (P = 0.003) patients. A similar linear decrease was observed in the esophageal and gastric cancer surgery subgroups. Between the low- and very-high-volume centers, an almost 70% reduction in the relative risk of POM was systematically observed, independent of Charlson score or tumor location.

Conclusions: To improve POM, esophageo-gastric cancer surgery should be centralized, irrespective of the patient’s condition or tumor location.

Legal entity responsible for the study: CHRU Lille

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

A phase III clinical trial of neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus

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Background: Preoperative chemoradiotherapy followed by surgery seems to hopefully improve the survival of locally advanced ESCC. Nevertheless, the results of different studies were inconsistent. We are to carry out a phase III clinical trial to investigate the effect of this multidisciplinary therapy for the overall survival of patients with locally advanced ESCC.

Methods: According to Sixth Edition AJCC Cancer Staging, patients with IB-III staged squamous cell carcinoma of the thoracic esophagus are randomly allocated to either preoperative chemoradiotherapy followed by surgery (arm A) or surgery alone (arm B). The intended number of randomized patients is 430, 215 per arm. In the arm A, Chemotherapy and radiotherapy are performed concurrently. Patients received two cycles of vinorelbine and cisplatin. Vinorelbine at 25 mg/m2 per day is administered in bolus infusion on d1, d8, d15 and d22. Cisplatin at 75 mg/m2 is administered by intravenously infusion on d1 and d22 (or 25 mg/m2 days 1 to 4 and 22 to 25). A total radiotherapy dose of 40 Gy is delivered in 20 daily fractions of 2.0 Gy each (given 5 d/wk for 4 weeks). McKNSW esophagectomy or Ivor Lewis esophagectomy will be performed 4-8 weeks after chemoradiotherapy. Two-field

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lymphadenectomy with total mediastinal lymph node dissection is performed during surgery. Primary outcomes are 3 and 5 years overall survival.

**Results:** From July 2007 to December 2014, 451 eligible patients were randomly assigned in eight cooperative cancer centers (224 cases in arm A, and 227 cases in arm B). The median follow-up time for surviving patients was 39.6 months. In arm A, 185 cases continued to undergo surgery after chemoradiotherapy. The rate of R0 resection was 98.4% (182/185) in arm A versus 91.2% (207/227) in arm B (P = 0.002). A pathological complete response was achieved in 80 of 185 patients (42.3%) who underwent resection in the arm A. The overall survival at 3 years in arm A was significantly higher than arm B (69.6% vs 62.4%; HR 0.71 [95% CI 0.52–0.98], log-rank P = 0.035).

**Conclusion:** Neoadjuvant chemoradiotherapy plus surgery improved survival among patients with locally advanced esophageal squamous cell carcinoma.

**Clinical trial identification:** NCT01216527

**Legal entity responsible for the study:** Sun Yat-Sen University

**Funding:** The Health Ministry of China, Sun Yat-sen University Clinical Research 3010 Program, National Science Foundation of China (NSFC), Science and technology fund or projects of Guangdong Province; Major science and technology special fund for projects of Zhejiang Province.

**Disclosure:** All authors have declared no conflicts of interest.

**Clinical next generation sequencing (NGS) of esophagogastric (EG) adenocarcinomas identifies distinct molecular subtypes of response to HER2 inhibition, first-line 5FU/platinum and PD1/CTLA4 blockade**

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**Background:** TCGA identified potential therapeutic targets unique to subtypes of EG adenocarcinoma including RTK alterations in CIN tumors and immunotherapy in EBV and MSI tumors.

**Methods:** Patients with Stage IV EG adenocarcinoma were analyzed using a NGS assay (MSK-IMPACT) capable of detecting somatic mutations (MUT), deletions and amplifications (AMP) with results correlated with clinical outcomes.

**Results:** We analyzed 429 tumors from 319 pts with Stage IV EG adenocarcinoma (33% esophagus, 52% gastric, 15% GEJ). 80 of 319 (25%) pts had HER2+ (IHC3+, IHC2+/FISH+) tumors: 71 collected pre-trastuzumab (T), 38 post-T, and 28 with paired pre/post samples. In the paired samples, we observed post-therapeutic loss of HER2 amplification (16%). Co-occurring EGFR/HER2 AMP were detected in the post-T tumors of 4 of 20 pts treated with trastuzumab with 3 achieving a PR. 20 of 319 pts (6%) pts had deleterious somatic (n = 15) alterations of HER2, including HER2 gain of new AMP of MET (7%), EGFR (4%), and IGF1R (4%); MUT in ERBB4 (14%), KRAS (11%), PIK3CA (7%), MTOR (7%). Co-occurring HER2 and EGFR mutations were much less common in SBA, representing only 18% of BRAF-mutated cases. Amplification of ERBB2 and EGFR was most common in GC and least common in SBA; however, both ERBB2 and EGFR point mutations were most frequent in SBA (7% and 1-4% of cases) compared to the other tumor types examined. MSI-high status was more frequent in SBA (6.9%) than in CRC (3.9%) and GC (4%). Overall, the molecular profile of unspecified SBA was similar to duodenal adenocarcinoma (DA). Targetable alterations in several additional genes including PIK3CA and MEK1 mutations and RTK fusions were also identified in all three series. One SBA patient with a G0P0-R0S1 fusion has an ongoing clinical response to crizotinib.

**Conclusions:** This study presents the first large scale genomic comparison of SBA with CRC and GC, as well as a comparison of unspecified SAs with tumors of the duodenum. Higher incidence of microsatellite instability in SBA suggests that an important subset of these patients may benefit from treatment with anti-PD-1/PD-L1 therapies. The use of CGP during the course of clinical care identifies targetable genomic alterations across intestinal tumor types and allows patients to be matched with appropriate targeted therapies.

**Legal entity responsible for the study:** Foundation Medicine, Inc.

**Funding:** Foundation Medicine, Inc.

**Disclosure:** A.B. Schrock, J. Sun, P. Stephens, J.S. Ross, V.A. Miller, S.M. Ali: Employee at Foundation Medicine. Stock ownership: Foundation Medicine. All other authors have declared no conflicts of interest.
Background: IMAB362, a chimeric monoclonal antibody that mediates specific killing of cancer cells expressing the tight junction protein Claudin18.2 (CLDN18.2) by activation of immune effector mechanisms, has demonstrated single-agent activity and tolerability in patients (pts) with heavily pretreated gastric cancer.

Methods: Pts with advanced, current gastric and G1I cancer were centrally evaluated for CLDN18.2 expression by immunohistochemistry (CLAUDETECT® 18.2 Histology Kit). Eligible pts had a CLDN18.2+ expression of ≥40% tumor cells, an ECOG ≤ 2, and were not eligible for trastuzumab. Pts were randomized 1:1 to first-line IMAB362 plus EOX (epirubicin 50 mg/m² and oxaliplatin 130 mg/m² d1, and capecitabine 625 mg/m² d1, qd21) with or without IMAB362 (loading dose 800 mg/m², then 600 mg/m² d1, qd21). An exploratory arm (N = 85) was added to investigate a higher dose IMAB362 (1000 mg/m²) plus EOX. The primary study endpoint was PFS (Arm1 vs 2, 95% CI, HR, p-value).

Results: Of 686 biomarker-assessable pts, 334 pts (48%) were tested CLDN18.2+ per results. Of those, 161 pts (median age 58 years, 80% gastric, 16% G1I, 4% esophageal, 44% diffuse, 33% intestinal) were randomized into Arms 1 and 2. IMAB362 plus EOX improved PFS (median 4.8 vs 7.9 months; HR 0.47; 95% CI, 0.31-0.70, 1-sided p = 0.0001). OS (median 8.4 vs 13.2 months; HR 0.51, 95% CI 0.36–0.73, p = 0.0001) and ORR (28% vs 43%) compared to EOX. Common IMAB362-related adverse events included vomiting, neutropenia, and anemia, which were mostly of NCI-CTCAE grade 1 or 2. Grade 3/4 events were not significantly increased by IMAB362.

Conclusions: This final analysis confirms that addition of IMAB362 to first-line chemotherapy provides a clinically relevant benefit in patients with inoperable or recurrent gastric G1I cancer.

Clinical trial identification: ClinicalTrials.gov NCT016530083

Legal entity responsible for the study: Ganymed Pharmaceuticals AG

Funding: Ganymed Pharmaceuticals AG

Background: REACH was a global, randomized, phase 3 study evaluating the efficacy and safety of single-agent RAM in pts with advanced HCC after sorafenib. While a significant median overall survival (OS) benefit was not observed in the ITT population (N = 563), a survival benefit was observed in pts with a baseline alpha-fetoprotein (AFP) ≥400 ng/mL (n = 250); OS: 7.8 vs 4.2 months (PBO; HR 0.67; P = .006). Ad hoc retrospective analyses on the survival and safety of pts by liver disease etiology were performed.

Methods: In each disease etiology subgroup (Hepatitis B [HepB], HepC, or Other) per protocol analysis of OS was performed using log-rank test and Cox proportional hazards model. The objective response rate (ORR) was defined as the proportion of pts with best overall response of CR or PR.

Results: Baseline pt characteristics were generally balanced between treatment arms in each subgroup. 37% were reported as HepB (n = 154), and 36% Other (n = 202). HepB pts were more likely to be Asian, ECOG PS 1, have extra-hepatic spread, and AFP ≥400 ng/mL. The OS for RAM compared to PBO was 8.2 vs 5.4 mo in HepB (HR 0.79; P < .001); 9.2 vs 8.0 mo in HepC (HR 0.89; P = .04); and 11.1 vs 8.5 mo in Other pts (HR 0.85; P = .33). ORR was 2.8% RAM vs 0% PBO in HepB pts, 10.3% vs 2.6% in HepC pts, and 9.1% vs 0% in Other pts. In pts with baseline AFP ≥400 ng/mL, the OS for RAM compared to PBO was 6.6 vs 4.0 mo in HepB (HR 0.67; P = .04) vs 4.8 mo in HepC (HR 0.89; P = .68) and 8.5 vs 4.3 mo in Other pts (HR 0.45; P = .003). In all subgroups with baseline AFP ≥400 ng/mL, no trend to survival benefit was observed. In all three etiology subgroups, the most common treatment-emergent adverse events of any grade included peripheral edema, fatigue, pyrexia, and ascites. Incidences of specific Grade ≥3 adverse events were generally low and similar among subgroups.

Conclusions: HepB pts had shorter survival compared to pts with HepC or Other. In all etiology subgroups with a baseline AFP ≥400 ng/mL, a potential improvement in survival with RAM was observed. RAM was well tolerated with a similar safety profile across all etiology subgroups.

Clinical trial identification: NCT0140347

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company


Molecular characteristics of hepatocellular carcinomas (HCC) from different age groups

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Background: HCC patients (pts) from the Western hemisphere are usually diagnosed in their 50s and 60s, whereas HCCs in young adults (YA, 18-39 years) and the elderly (E, ≥75 years) are less common. Worldwide, HCCs diagnosed at extremes of the age spectrum are associated with distinct geography and etiologies. Multiparametric profiling data were used to compare molecular characteristics of HCCs of different age groups.

Methods: Gene sequencing, amplification and protein expression data on 421 HCC specimens were reviewed and stratified into YA, E, and intermediate age (IA, 40-74 years) subgroups. Only pathogenic or presumed pathogenic (P/P) mutations were analyzed. The Chu-square test was used for statistical comparisons. Etiologies are being collected.

Results: There were 39 YA, 336 IA and 46 E pts. Female prevalence was higher in YAs (54%) vs IA (23%) (p < 0.0001) and E pts (33%, p < 0.0485). In males, androgen receptor (AR) expression was lower in YAs (6%) vs IA (35% (p = 0.02) and E (32%, p < 0.05); in females, AR tended to increase with age (6%, 7% and 15%, p = 0.055).
MRP1 expression decreased in YAs (69%) vs IA (86%; p = 0.04) and E pts (95%, p = 0.02). MGMT was higher in IA than YA (71% vs 49%, p = 0.007) and SPARC higher in E than YA (13% vs. 0%, p = 0.005). PDGFR and PD-L1 were expressed in IA (14% and 19%) and E pts (29% and 17%) but not in LV. Of 47 cases analyzed, TP53 was the most frequent alteration in YAs (19%) while CTNNB1 was the most frequent in E (33%) and IA (30%) and only 9.5% in YA. PIK3CA, PTEN, and PTPN11 mutations were more prevalent in E (13.3%, 7.1% and 6.7%, respectively) vs IA pts (1.4%, 0.7% and 0%, all p < 0.05) and were absent in YA. An ATM mutation occurred in 1/21 YAs, but not in IA (0/14) or E (0/21). The overall frequency of PP mutations was lower in YAs (0.38 mutation/case) vs. IA (0.71, p = 0.012) and E (0.93, p = 0.038).

Conclusions: HCCs from YAs were associated with female sex, decreased drug resistance protein and AR expression. YAs may be more sensitive to alkylating agents whereas E pts may be more sensitive to PIK3CA/Akt/mTOR or MAPK pathway inhibitors. Our results provide important knowledge to prospective studies among a network of cancer centers that will also incorporate etiological factors and molecular features into investigations for HCC therapies.

Legal entity responsible for the study: Celina Ang

Funding: N/A

Disclosure: J. Xiua, Z. Gatalica, S. Reddy: Employee of Caris Life Sciences. All other authors have declared no conflicts of interest.

Method: Molecular profiles—using protein expression (IHC), gene amplification (ISH) and sequencing—of PC tumors were reviewed and correlated with pt outcomes. A Chi-squared test determined differences between age groups; Kaplan-Meier methodology estimated survival.

Results: In total, 242 PC tumors were examined. The most frequently mutated genes were KRAS (85%), TP53 (63%), SMAD4 (13%), BRCAl2 (12%), ATM/PAPC/NTRK1 (5%) each), BRCAl4 (4%), and cMET/PIK3CA (3%) each subgroup analysis of tumors from 5-year younger (median age: 50; range: 15-55) and 51-year older (71, 65-90) pts was performed. When compared with older pts, younger pts’ tumors had a greater frequency of mutations in MLH1 (4% vs. 0.3%, p = 0.003), PTEN (3% vs. 0.5%, p = 0.008), EGFR (2.2% vs. 0%, p = 0.003), CTNNB1 (2.3% vs. 0.5%, p = 0.04), c-KIT (2% vs. 0%, p = 0.02), and NTRK1 (20% vs. 0%; p = 0.02; assessed in only 10 and 45 pts, respectively), whereas KRAS mutations were significantly higher in older pts (80% vs. 70%; p = 0.003). The mutation rates (older vs. younger) of BRCAl (both 5%), BRCAl2 (14% vs. 12%), BRAF (both 1%), GNAS (2.4% vs. 1.6%), PIK3CA (both 3%), NOTCH1 (0.9% vs. 1.6%), cMET (2.8% vs. 3.9%), and RET (0.4% vs. 0.8%) were similar in both age groups. Older pts’ tumors had higher rates of low RBM1 expression (83% vs. 79%, p = 0.03) and high PDGR expression (22% vs. 7%, p = 0.03), whereas younger pts had higher TOP2A expression (59% vs. 50%, p = 0.02). There was no difference in either PD-L1 expression in tumor cells (8% vs. 7%) or the frequency of PD-1 expression on tumor infiltrating lymphocytes (41% vs. 37%). Outcomes were evaluable for 73 pts. There were no survival differences between the two age groups. Low ERCC1, MGMT, PRM1, and TLE3 expressions appeared to be associated with prolonged survival in older but not younger pts; however, larger studies are needed to define the significance of this finding.

Conclusions: Young pts with PC may carry genetic alterations that are different from older pts. A wider gene panel is needed to aid in the discovery of targeted mutations and provide therapeutic opportunities.

Legal entity responsible for the study: Georgetown University

Funding: N/A

Disclosure: R. Feldman, J. Xu, S. Reddy, Z. Gatalica: Employment by Caris L.S. All other authors have declared no conflicts of interest.

Methods: Randomization phase II study of S-1 and concurrent radiotherapy with versus without induction chemotherapy of gemcitabine for locally advanced pancreatic cancer (LAPC).

Results: Final analysis of JCOG1106

Background: JCOG1106 is a phase II trial to evaluate the efficacy and safety of chemoradiotherapy (CRT) with and without induction chemotherapy (CT) to determine which is more promising CRT regimen for LAPC. Primary endpoint was overall survival (OS). 102 patients (pts) were randomized to CRT (Arm A) or induction CT followed by CRT (Arm B), and 100 pts (Arm A/B = n = 51/49) were eligible. In the primary analysis performed 1 year after completion of enrollment, 1-year OS for Arm A/B were reported to be 66.7/69.3% (hazard ratio [HR] 1.16), and Arm B was considered more promising based on pre-specified decision rule (J Clin Oncol 33, 2015, suppl, abstr 4119) and the probability of survival greater in Arm B in the first 12 months, there was a possibility that it would be greater in Arm A in the following period. We performed final analysis 1 year after primary analysis.
Results: After 382 events, median OS was improved with nal-IRI + 5-FU/LV vs 5-FU/LV (6.2 vs 4.2 mo; HR 0.75; 95% CI 0.57-0.99; P = 0.038), but not for nal-IRI vs 5-FU/LV (4.9 vs 4.2 mo; HR 1.07; 95% CI 0.84-1.36; P = 0.567). Kaplan-Meier estimates of OS for nal-IRI vs 5-FU/LV and 5-FU/LV, respectively, were 53% and 38% at 6 mo, and 28% and 16% at 12 mo. Median progression-free survival was longer for nal-IRI + 5-FU/LV vs 5-FU/LV (3.1 vs 1.5 mo; HR 0.57; 95% CI 0.43-0.76; P < 0.001), but not for nal-IRI vs 5-FU/LV (2.7 vs 1.6 mo; HR 0.81; 95% CI 0.63-1.04; P = 0.111). Response rates per RECIST v1.1 were higher for nal-IRI + 5-FU/LV vs 5-FU/LV (17% vs 1%; P < 0.001) and for nal-IRI vs 5-FU/LV (6% vs 1%; P = 0.020). Grade ≥3 treatment-emergent adverse events ≥10% of pts in either nal-IRI arm were neutopenia (26%, 15%, and 1% in the nal-IRI + 5-FU/LV, nal-IRI, and 5-FU/LV arms, respectively), fatigue (14%, 6%, and 4%), diarrhea (13%, 21%, and 5%), vomiting (12%, 14%, and 4%), anemia (9%, 11%, and 7%), and hypokalemia (3%, 12%, and 2%).

Conclusions: Final results from NAPOLI-1 continue to show OS benefit for nal-IRI + 5-FU/LV vs 5-FU/LV. No new safety concerns were identified. nal-IRI + 5-FU/LV provides a new treatment option for pts with mPAC previously treated with gemcitabine-based therapy.

Clinical trial identification: NCT01494506

Legal entity responsible for the study: Merrimack Pharmaceuticals, Inc.

Funding: Merrimack Pharmaceuticals, Inc.


Multimodality treatment (MMT) and outcomes of gastric adenocarcinoma (GC) in National Cancer DataBase(NCDB)

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Background: In patients (pts) with non-metastatic GC, MMT added to surgery improves the cure rate. The MMT includes adjuvant chemotherapy (ACR), neoadjuvant chemoradiation (NACR), and peripерoperative chemotherapy (CT). We used the NCDB data to compare different MMT in pts with non-metastatic GC.

Methods: A total of 79369 pts with non-metastatic GC diagnosed 2004–2013 were identified. Pts with known tumor size who underwent surgery and received MMT were selected for this analysis. Treatment included NACR, CT, and ACR. Pts divided into two cohorts cardia GC (cGC) and non-cardia GC (nGC). Among 10796 pts with cGC and 10683 with nGC, demographics, tumor characteristics, and treatment data were abstracted. Overall survival (OS) was selected as the primary study outcome. Cox regression model was used to examine the effect of choice of MMT on OS adjusting for all known prognostic factors.

Results: Summary of results included in the table. In 10796 pts with cGC MMT distribution was 24%, 55%, and 21% for ACR, NACR, and CT. These numbers for nGC were 10681, 35%, 7%, and 38%. OS in the treatment groups: cGC 42.1 (95%CI: 40.2-44.1), NACR 35.9 (95%CI: 34.2-37.9), and CT 34.2 (95%CI: 32.7-35.8). In cGC, ACR remained superior with median OS of 36.4 (95%CI: 35.4-39.0) vs. NACR 34.0 (95%CI: 32.5-35.6; HR 1.11) and CT 33.3 (95%CI: 31.2-35.6; HR 1.11) < 0.001. These number for nGC were 48.3 (95%CI: 46.5-50.2), 35.1 (95%CI: 31.0-40.9; HR 1.18), and 35.9 (95%CI: 33.5-38.3; HR 1.21) < 0.001. In the cGC, CT resulted in a significant (p < 0.001) reduction in the size of the tumor with the median tumor size of 4 cm as compared to 4.5 cm in the ACR, there was no difference in the size of the tumor between CT and ACR group for nGC.

Table: 623P

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<td><strong>N (%) (cGC, nGC)</strong></td>
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<td><strong>Mean Age</strong></td>
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Conclusions: ACR increased the odds of survival by 20% in the nGC and by 10% in cGC pts. Although this is a retrospective analysis the large sample size and long follow up provides confidence in the observation. There is a statistically significant difference in

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**Abstracts**

**Methods:** Pts in Arm A received RT (50.4 Gy/28 fr) with concurrent S-1 (40 mg/m²/ dose, b.i.d. on the day of irradiation). Pts in Arm B received induction gemcitabine (1.000 mg/m² iv, days 1, 8, 15, every 4 weeks) for 12 weeks, and then, only pts with controlled disease received same CRT as Arm A. After CRT, GEM was continued until disease progression or unacceptable toxicity in both arms. Decision rule was set as follows: Arm A, which was expected to be less-toxic, will be considered more promising if point estimate of HR for OS of Arm B to Arm A is smaller than 1.16.

**Results:** In the final analysis, 2-year OS for Arm A/B were 36/198/9% and HR was 1.26 [95%CI 0.82-1.93]. 2-year progression-free survival were 6/4/2/4% (HR 1.03), and 2-year distant metastasis-free survival were 14/84/2% (HR 1.25). Incidences of grade 3/4 toxicities in Arm A/B were leukopenia 62/61%, neutropenia 54/57%, anemia 18/12%, thrombocytopenia 10/14%, anorexia 16/4%, fatigue 8/4%, nausea 8/2%, diarrhea 6/4%, gastroduodenal (GD) hemorrhage 10/6%, GD ulcer 6/4%, and biliary infection 20/27%. Three treatment-related deaths occurred in Arm A (pneumonitis, GD hemorrhage, biliary infection). **Conclusions:** Compared to CRT alone, CRT with Induction CT of gemcitabine resulted in a poorer long-time outcome, in spite of a favorable short-time outcome.

**Clinical trial identification:** UMIN000088611

**Legal entity responsible for the study:** Akira Fukutomi

**Funding:** Grants from MHLW, Japan. Grants from Japan AMED

Background: In GC an urgent need exists for effective targeted therapies and predictive markers. In a PhII study, low ATM expression in tumour was associated with greater overall survival (OS) benefit in GC patients treated with olaparib/paclitaxel (1). Antibodies targeting the programmed death-1 checkpoint have reported clinical efficacy in GC, with tumour PD-L1 expression and microsatellite instability (MSI) emerging as predictive markers. We have assessed the prognostic significance of PD-L1 and immune infiltrates in GC and their association with the ATM-low segment.

Methods: PD-L1, CD3+ T-lymphocytes, CD8+ cytotoxic T-cells, human epidermal growth factor receptor 2 (HER2) and ATM expression were assessed by immunohistochemistry (IHC) in a cohort of 384 Korean gastric cancers.

Results: PD-L1 positivity (>9%) on tumour cells (TC) and immune infiltrates (IC) was 16% and 90% respectively and a correlation was observed with MS (p < 0.01) and immune infiltrates (CD3 P < 0.05; CD8 P < 0.01). PD-L1 TC and CD8 were not associated with Lauren subtype. Multivariate analysis showed PD-L1 TC positivity, CD3 and CD8 were significantly associated with better OS (p < 0.01) and disease free survival (p < 0.01). Prevalence of HER2-high (IHC 3+) was 7% and ATM-low (<10% TC positive) was 11.5%. These segments were largely mutually exclusive; only 1/27 HER2-high had also ATM-low. The majority (99%) of HER2-high tumours were microsatellite stable (MSS) with a trend for lower prevalence of PD-L1 (7.4% vs 17%) and CD8 (11.5% vs 21%) compared to HER2-low. The ATM-low segment was significantly enriched for PD-L1 (p < 0.01), CD8 (p < 0.05) and MSI (p < 0.01) compared to ATM-high, but heterogeneous with 46% ATM-low tumours being MSS and 65% PD-L1 TC negative.

Conclusions: In GC PD-L1, CD3/CD8 are prognostic for better outcome. Mutually exclusive ATM-low and HER2-high segments differ in their immune profile, with the immunologically hot ATM-low segment enriched for MSI, PD-L1 and CD8. This illustrates the opportunity to employ different strategies for maximising the benefit from immune therapies in HER2 and ATM segments. (1) Bang et al. (2015) JCO 33:3858-3865

Legal entity responsible for the study: AstraZeneca and Samsung Medical Center

Disclosure: E. Kilgour, H. Angell: Employee and holds stock in AstraZeneca. AstraZeneca and Samsung Medical Center, Boston, MA, USA

Methods: Data was collected from 30 European centers from 2000–2010. 2489 EC patients surgically treated were included in the PEC group and 136 in the ECRF group, including 61 in the NRIEC group and 75 in the RIEC group. Propensity score matching analyses were used to compensate for differences in baseline characteristics.

Results: Compared to the PEC group, the ECRF group was characterized by a higher use of neoadjuvant chemoradiotherapy (0% vs 29.5%; P = 0.001), less pathological stage II/IV (31.6% vs 39.2%; P = 0.036), greater incidence of R1/2 margins (21.3% vs 10.9%; P < 0.001), increased in hospital mortality (14.9% vs 7.1%; P = 0.035) and overall morbidity (68.4% vs 56.4%; P = 0.068). After matching, 5-year overall survival (28.8% vs 50.5%; HR = 1.53, 95% CI 1.15-2.04; P = 0.003) and event-free (32.2% vs 42.5%; HR = 1.36, 95% CI 1.18-2.05; P = 0.002) survivals were significantly reduced in the ECRF group. There were no significant differences in incidence or pattern of tumor recurrence. Comparing RIEC and NRIEC groups, there were no significant differences in short- or long-term outcomes before and after matching.

Conclusions: ECRF is associated with poorer long-term survival related to a reduced utilization of neoadjuvant chemoradiotherapy and an increased incidence of tumor margin involvement at surgery. Outcomes are dictated by the limitations related to previous radiotherapy administration more than the radiotherapy-induced carcinogenesis.

Legal entity responsible for the study: N/A

Disclosure: All authors have declared no conflicts of interest.
Background: Neoadjuvant chemotherapy (neoCTX) improves the prognosis of patients (pts) with localized esophageal adenocarcinoma (EAC). This retrospective analysis evaluates the predictive value of histopathology on neoCTX.

Methods: 661 pts with locally advanced EGC (T2/T3 and/or N+) who received neoCTX followed by surgery between 2000 and 2013 were analyzed from four institutions: 314 (68.1%) with intestinal, 94 (20.4%) with diffuse and 53 (11.5%) with mixed histological type according to Laurens classification. Taxane-platinum- fluoropyrimidine (SFU) based triple or platinum-FU based doublet neoCTX was administered preoperatively to 185 (40.4%) and 276 (59.9%) pts, respectively. Pathological response evaluation according to Becker was performed locally.

Results: Median patients’ age was 63 years, 79.8% were male. Tumors were localized in the stomach in 32.5% and EGC junction in 67.5%. 96.5% had clinical stage T3/T4 and 93.7% were N+. With a median follow up of 36.9 months (mos), median overall survival (OS) was 66.4 mos. For pts with intestinal type, median OS was 77.9 mos compared to 34.6 mos for diffuse (p = 0.001) and 64.4 mos for mixed type (p = 0.657). Median disease-free survival (DFS) was 48.7 mos for intestinal compared to 17.3 mos for diffuse (p = 0.002) and 29.2 mos for mixed type (p = 0.327). Pathological complete response (pCR) was 9.1% and combined complete and subtotal response (pCR + pSR) was 26.7% for all pts. 25/26 (96.9%) of pts with intestinal type had a pCR compared to 4/65 pts (6.2%) with diffuse and 4/37 (10.8%) with mixed type. pCR + pSR rate was significantly higher in intestinal (30.3%) compared to diffuse (15.4%; p = 0.024), but 4/65 pts (6.2%) with diffuse and 4/37 (10.8%) with mixed type. pCR + pSR rate was significantly higher in intestinal (30.3%) compared to diffuse (15.4%; p = 0.024), but 4/65 pts (6.2%) with diffuse and 4/37 (10.8%) with mixed type.

Conclusions: Pathologic complete response is associated with long-term survival in EGC independent of histopathological subtype. Efforts to increase the rate of pCR by more effective neoCTX are warranted.

Legal entity responsible for the study: Technical University Munich

Funding: Technical University Munich

Disclosure: F. Lordick: Receipt of grant/research supports: GSK, Fresenius Biotech, Boehringer. Receipt of honoraria or consultation fees: Amgen, Eli Lilly, Garrymed, MSD. Mercè Serono, Roche, Taiko. Travel support: Bayer, MSD, Amgen, Roche. All other authors have declared no conflicts of interest.

The role of antiangiogenic therapy in advanced gastro-esophageal cancer: a systematic review and meta-analysis

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Background: Antiangiogenic therapy (AT) has demonstrated a significant improvement in overall survival (OS) in advanced gastro-esophageal cancer (AGC) in the second line (2L) setting. However results in the first line (1L) are unalike and its role is still unclear. The small size of the majority of the studies may be underestimating the effect of this treatment. We aimed to perform a systematic review and meta-analysis of randomized clinical trials (RCT) in this setting to synthesize the available data and help decision-making.

Methods: A systematic search was performed through MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and ASCO meeting abstracts up to April 2016 to identify RCTs for AGC comparing standard treatment alone in 1L and 2L. Studies were reviewed by two authors and discrepancies were resolved by consensus or by a third author. Data including progression-free survival (PFS), OS and response rate (RR) were extracted. The primary endpoint was OS. A meta-analysis (MA) with fixed and random effects models comparing the different regimens with direct comparisons was conducted.

Results: Ten RCT including 2767 patients were identified. Six evaluated AT in 1L and four in 2L. Overall, the pooled analysis demonstrated that AT improved OS (HR = 0.84, 95% CI 0.77-0.92) and PFS (HR = 0.74, 95% CI 0.61-0.89). When 1L and 2L RCT were analyzed separately, a statistically significantly improvement in OS (HR = 0.79, 95%CI 0.70-0.89, p = 0.001) and PFS (HR= 0.56, 95% CI 0.45-0.70, p < 0.001) was seen in 2L favouring the AT containing arm compared to non-AT. However, no statistically significant differences in OS (HR = 0.9, 95%CI 0.70-1.03) or PFS (HR= 0.96, 95% CI 0.81-1.15) were demonstrated in 1L. No significant heterogeneity was found among RCTs.

Conclusions: The results of direct MA suggest that AT vs. non-AT improves OS and PFS in patients in the 2L setting for AGC, however no benefit was demonstrated in the 1L.

Legal entity responsible for the study: Hospital Universitario 12 de Octubre

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Molecular characterization of HER2-positive (HER2+) metastatic gastric and gastro-esophageal junction cancer patients (mGC): Identification of resistance mechanisms to trastuzumab-based therapy (TTZ)

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Background: mGC represents the 3rd leading cause of cancer death worldwide. Chemotherapy is efficient but limited, overall survival (OS) of mGC patients (pts) remains poor. Almost 40% of them harbor ERK and PI3KCA pathway gene amplifications (amp). HER2+ mGC patients benefit from TTZ, however response is seen in <50% and not durable in time. We aim to study potential molecular determinants of TTZ resistance.

Methods: We analyzed baseline biopsies of 105 HER2+ mGC pts from 10 Spanish hospitals. All pts received TTZ. Median follow up was 13 months (m), 22m for alive pts. We evaluated Cyclin E1/D1 and PI3KCA amp (Fluorescence In Situ Hybridization), expression of cyclin E1/D1, PTEN, HER2 and p95HER2 (immunohistochemistry-IHC), HER2 and p95HER2 quantification (Ventana fluorescence assays), and PI3KCA mutations (Sanger sequencing).

Results: The median age of pts was 65 years (63–67), 75% men. Location of primary tumor was gastric (57%) and gastro-esophageal (43%). The most common histologies were intestinal (74%) and diffuse (13%). Predominant metastatic locations were liver (33%), lymph nodes (30%), peritoneum (14%) and lung (10%). Median OS was 12.8m (10.6-13.4). Median progression-free survival was 7.3m (6.7-7.9). Amp (gene/CEP 2) were found in cyclin E1 (21%) and cyclin D1 (15%). A positive correlation between amp/overexpression was detected for cyclin E1 (<0.001), but not for cyclin D1 (p = 0.37). PTEN expression was low (Hscore = 1-4) in 12.4% and undetectable (Hscore = 0) in 57% HER2 was overexpressed in 36.7% (Hscore ≥ 3 in ≥ 10% of cells). There was a positive correlation between levels of p95HER2 and HER2. PI3KCA amp/ mut were found in 4% and 2%, respectively. Survival analyses according to molecular findings will be presented.

Conclusions: To our knowledge, this is the largest molecular characterization of HER2-positive mGC pts. Whereas levels of HER2 have been associated with intrinsic sensitivity to TTZ, cyclin E1/overexpression has been described as a TTZ resistance mechanism in breast cancer. Final survival analysis will shed light of the real role of these molecular alterations in HER2+ mGC.

Legal entity responsible for the study: VHO Vall d’Hebron Institute of Oncology

Funding: VHO Vall d’Hebron University Institute of Oncology

Disclosure: J. Tabernero: Consultant/Advisory role: Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Merck Serono, Novartis, Roche, Sanofi, Symphogen, Takeda, Taiho. All other authors have declared no conflicts of interest.
Clinical significance of serum factors relating to ERBB signaling pathways in a phase II trial of S-1 plus cisplatin combined with trastuzumab for HER2-positive advanced gastric or esophagogastric junction cancer: WJOG7212G (T-SPACE) TR study


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Background: No biomarker other than HER2 expression for anti-HER2 therapy has been established in gastric cancer. We explored serum ERBB-related biomarkers for efficacy in a phase II trial (WJOG7212G) of triweekly trastuzumab (Tmab) (first dose 8 mg/kg then 6 mg/kg) in combination with S-1 (40-60mg, twice daily, for 21 days) plus cisplatin (60 mg/m², on day 8) for HER2-positive (IHC3 +, or IHC2+ and FISH+) advanced gastric or esophagogastric junction cancer. Methods: Serum samples were collected in 31 of 44 patients enrolled in the phase II study. Serum HER2, EGF, TGF-alpha, neuregulin 1 (NRG1), HGF, IGF1 and TIMP1 were measured by ELISA at following 4 points: pre-treatment, immediately before 2nd and 4th Tmab administration, and after PD. Free survival (PFS) and overall survival (OS) were compared between the high and low groups defined as a median of pretreatment value of each serum marker. Results: Patient characteristics were: median age 65.0 years, males 23 (74%), PS 0–1 29 (93%), primary site of stomach 27 (87%), histology of diffuse type 14 (45%), IHC3 + 22 (71%) patients. The response rate was 69% (95% CI 50 – 81). The median PFS was 183 days (95% CI 133 – 420). The median OS was 515 days (95% CI 373 – not reached). Pre-treatment HER2 and NRG1 levels were higher in responders than in non-responders (median 96.8 vs 68 ng/ml, p = 0.036, NRG1 2467 ± 886 ng/ml vs 186 ± 186 ng/ml, p = 0.012). HER2, NRG1 and EGF levels decreased after treatment (p < 0.05). Patients with high pre-treatment NRG1 levels showed significantly longer PFS (median 322 vs 160 days, p = 0.022) and marginally decreased after treatment (p < 0.05). Patients with high pre-treatment NRG1 levels showed significantly longer OS (median 373 days, p = 0.039) than those with the low levels. Pre-treatment HER2 level was not associated with either PFS (median 247 vs 177 days, p = 0.50) or OS (median 544 vs 503 days, p = 0.53). Conclusions: Serum NRG1 may be a candidate of a predictive marker for the efficacy of Tmab in combination with S-1 plus cisplatin in patients with HER2 positive gastric or esophagogastric junction cancer. Clinical trial identification: Protocol number: UMIN000008839, Release date: 9, July, 2012. Legal entity responsible for the study: West Japan Oncology Group Funding: Taibo Pharmaceutical Co.Ltd. Disclosure: Y. Murakata: Honoraria: Kyowa Hakko Kirin, Novartis. T. Takano: Honoraria: Chugai, Taibo. K. Yamazaki: Honoraria: Chugai, Taibo. S. Hirotsuka: Honoraria: Taibo. N. Boku: Honoraria: Taibo. M. Ito: Honoraria: Taibo. B. Kato: Honoraria: Taibo. B. Myers: I. Hyodo: Honoraria: Daiichi-Sankyo, Chugai, Taibo. Y. Pokuro: Yakult Pharmaceutical Companies. All other authors have declared no conflicts of interest.

The role of cardiovascular risk factors on postoperative course after esophageal cancer surgery

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Background: After an esophagectomy vascularization of the gastric conduit is provided only by the right gastric artery. It is admitted that the risk of anastomotic leakage (AL) is increased by a low blood supply. Patients with esophageal cancer have frequently an impaired cardiac function and/or a atherosclerotic vascular disease (AVD). No data has previously emerged from studies regarding the role of cardiovascular risk factors (CRF) in patients who developed anastomotic leakage (AL) after esophagectomy in curative intent. The main objective was to determine if CRF can predict AL after Ivor-Lewis procedure in patients with intrathoracic esophageal cancer (EC).

Methods: We performed a retrospective study including all 352 consecutive patients operated on for EC in a curative intent between 2004 and 2014 in 2 referral centers. Patients treated by Ivor-Lewis procedure were analyzed. Nine CRF were identified according international consensus. Dindo Clavienn classification was used to define postoperative complication. Predictive factors of AL were analyzed by multivariable regression analysis.

Results: Among 292 patients with EC treated with Ivor-Lewis procedure, 271 (92.8%) patients had one or more CRF. The median age was 64 years (range, 33 – 85), with a male to female sex ratio of 4.4:1. Squamous cell carcinoma (SCC) was present in 141 (73.8%) patients. Among the 111 (38%) patients with postoperative complications, 39 (13.4%) patients developed anastomotic leakage, 15 (5.1%) developed necrosis of the gastric conduit. Others main complications were pneumonia (n = 37 patients; 12.7%), chylothorax (n = 13 patients, 4.5%) and hemorrhage (n = 7 patients, 2.4%). In multivariate analysis, transfusion (odd ratio: 3.030, 95% CI [1.545 – 5.952], p = 0.001) and CRF > 3 (odd ratio: 2.958, 95% CI [1.132 – 7.751], p = 0.027) were predictive factors of AL.

Conclusions: Patients with >3 CRF have a higher risk of AL after Ivor-Lewis procedure. Further studies should focus on how to improve postoperative outcomes in this population.

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KRAS mutation and protein levels in gastric cancer patients and response to MEK inhibitors

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Background: Recent studies have suggested that KRAS plays an important role in gastric cancer. The aim of this study was to assess the prognostic effect of KRAS mutation and expression levels in gastric cancer patients and to explore its potential role in targeted therapy.

Methods: We examined KRAS protein levels in 132 stage I-IV gastric cancer using immunohistochemistry. KRAS mutation was detected by next generation exome sequencing. KRAS mutation was examined in five human gastric cell lines (AGS, SNU601, SNU668, KATO-III and NUGC-4) by Sanger sequencing. Cytosensitivity of MEK inhibitors (AZD6244) in the five cell lines was examined by MTT.

Results: The median age of the total number of 132 gastric cancer patients was 58 years (range: 30-82). There were 75 gastric cancer samples with the pathology of signet-ring cell carcinoma (SRCC), while another 57 samples with adenocarcinoma. 80% of gastric SRCC samples have high expression of KRAS protein compared with 34.69% of gastric adenocarcinomas (P < 0.001). Among 75 gastric SRCC cancer patients, KRAS mutations in codon 12 and 151 were detected in 8 (10.67%) patients, including 7 mutations of G12V and one mutation of G151A. Kato-III and NUGC-4 cell expressed higher KRAS levels compared to the other three, while KRAS mutation was detected in AGS, SNU601 and SNU668. Two GC cell lines with KRAS mutation were hypersensitive to the MEK inhibitor compared with KRAS wild type cell lines. The median overall survival (OS) was 12.5 months (95% CI = 9.57 to 15.43 months) for patients with KRAS mutation, and 15.8 months (95% CI = 11.76 to 19.84 months) for patients without KRAS mutation (P = 0.031). However, no difference in OS was observed between low and high KRAS protein levels.

Conclusions: KRAS is highly expressed in SRCC. Patients with KRAS mutations have shorter OS. Gastric SRCC cell lines with KRAS mutation are sensitive to MEK inhibitor (AZD6244). The results provide insights into the important role of mutant KRAS in the prognosis and response to MEK inhibitor of gastric SRCC patients. Legal entity responsible for the study: Jia Wei Funding: Nation Science Foundation Disclosure: All authors have declared no conflicts of interest.
Efficacy and safety of dose-dense taxotere cisplatin fluorouracil regimen (mTCF-dd) in a large cohort of patients (pts) with metastatic or locally advanced non-squamous gastrointestinal cancer (GEC)

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Background: TCG is one of the most effective first-line options in metastatic GEC. We previously reported the significant activity of mTCF-dd (Tomasselli G et al. Gastric Cancer 2014 Oct;17(4):711-7). Aim of this study is to describe clinical outcomes, safety and studying potential clinical prognostic factors of this intensified regimen in a very large cohort of pts from a single center.

Methods: 201 consecutive pts with measurable or evaluable GEC treated in the same institution were longitudinally followed. 136 were enrolled in 3 different Clinical Trials and 65 treated according to clinical practice. We considered pts with PS ECOG 0-2 and adequate organ function who received from 2004 to 2015 mTCF-dd: Docetaxel (50-85 mg/m2 d 1), Capcitabine (50-75 mg/m2 d 1), L-Folinic Acid (100 mg/m2 d 1-2), 5-FU (400 mg/m2 bolus d 1-2, and 600 mg/m2 as a 44 h c.i. d 1) plus Pegfilgrastim 6 mg s.c. d 2-3. DM is defined according to IIT principles.

Results: Median age was 63 (range 25-81), M:F 1:1. Median OS was 33.4 months (95% CI 28.1-40.3). Median OS was 11.1 months (95% CI 9.5-13.5). Most frequent grade 3/4 toxicities: neutropenia (66%), anemia (31%), thrombocytopenia (17%), hypokalemia (16%), diarrhea (13%), febrile neutropenia (11%). 18 pts (9%) became resectable after mTCF-dd and underwent surgery. Finally, we identified 18 pts (9%) [12 metastatic, 6> localized] which were alive after a median follow-up of 50 months.

Conclusions: mTCF-dd in GEC is an effective and feasible option. A careful monitoring of adverse events is recommended. A biomolecular analysis of long-term survivors is underway.

Disclosure: R. Passalacqua: Member of Scientific Boards: Amgen, Lilly, Pfizer, MEDEA ONLUS

Funding: Eli Lilly and Company

Results:
PR, 14% SD, 13% PD and 13% NE, for an ORR of 59% (95% CI 52-66); DCR was 76%.

Method:
5-FU (400 mg/m2 bolus d 1-2, and 600 mg/m2 as a 44 h c.i. d 1), Cisplatin (50-75 mg/m2 d 1),l-Folinic Acid (100 mg/m2 d 1-2), 5-FU (400 mg/m2 bolus d 1-2, and 600 mg/m2 as a 44 h c.i. d 1), plus Pegfilgrastim 6 mg s.c. d 2-3. DM is defined according to IIT principles.

Results:
Median OS was 11.1 months (95% CI 9.5-13.5). Most frequent grade 3/4 toxicities: neutropenia (66%), anemia (31%), thrombocytopenia (17%), hypokalemia (16%), diarrhea (13%), febrile neutropenia (11%). 18 pts (9%) became resectable after mTCF-dd and underwent surgery. Finally, we identified 18 pts (9%) [12 metastatic, 6 localized] which were alive after a median follow-up of 50 months.

Conclusions: mTCF-dd in GEC is an effective and feasible option. A careful monitoring of adverse events is recommended. A biomolecular analysis of long-term survivors is underway.

Legal entity responsible for the study: Azienda Socio Sanitaria di Cremona

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Association of disease measurability, quality of life (QoL) and tumor status in patients (pts) with previously treated advanced gastric or gastroesophageal junction (GEJ) cancer

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Background: Hereditary diffuse gastric cancer (HDCG) is an autosomal dominant susceptibility for diffuse gastric cancer. Germ line mutation of CDH1 is observed in 30-50% of the HDCG, however, disease susceptibility genes have not yet identified in remaining 50-70%. Project HOPE is a comprehensive genetic analysis project including whole exome sequencing and gene expression analysis using fresh frozen samples obtained from various patients undergoing surgery in Shizuoka Cancer Center. In order to evaluate the genetic alterations in diffuse gastric cancer with family history, genetic analysis results were compared between patients with and without family history.

Methods: Of 188 patients registered in HOPE project, 51 patients with diffuse gastric cancer were included. In these patients, results from exome sequencing and gene expression analysis were compared between patients with family history (FDGC) and those without family history (NFDGC). Family history was defined as the presence of two or more documented cases of diffuse gastric cancer in first- or second-degree relatives OR solitary diffuse gastric cancer diagnosed prior to age 40 years. Whole exome sequencing was performed using Ion Proton to identify tumor specific gene mutations and to estimate the copy number with lymphocytes as normal control. Gene expression analysis was performed using DNA Microarray with adjacent normal tissue as a control.

Results: Three patients were classified to FDGC and 48 were to NFDGC. FDGC were tended to be younger, predominantly female and more advanced stage than NFDGC. Germ line mutation of CDH1 was not observed. Diffuse gastric cancer were separated into two groups, 27 patients with FDGC and 24 patients without FDGC, by gene expression profiling. In patients including FDGC, gene expression of PPP1R14C, ABCG2, NR1H2, APOC2, MLLT7-AS1 and PRB2 was observed. In somatic mutation analyses, the incidence of RHOA and CDH1 mutations was higher in patients with FDGC (19% vs 4%, 22% vs 13%). CDH1 mutation was observed in 2 of 3 FDGC.

Conclusions: Gene cluster that was highly expressed in FDGC was identified. Diffuse gastric cancer was classified into two groups by cluster analysis with these genes. Somatic mutation of CDH1 was frequently observed in patients group with distinctive family history.
Background: Ramucirumab, an anti-VEGFR2 monoclonal antibody, improved the outcome of MGC pts both as a single agent and in combination with paclitaxel, achieving recent approval in second-line therapy. However, few “real life” data are available. The objective of the RAMoss study is to evaluate the safety and efficacy of ramucirumab in the Italian compassionate-use program, prior to marketing authorization.

Methods: The primary endpoint was safety and secondary were overall response rate (ORR), progression free-survival (PFS) and overall survival (OS). Pts received ramucirumab 8 mg/kg every 2 weeks in combination with paclitaxel 80 mg/m2 every 3 weeks, on days 1, 8, and 15 of a 28 days cycle until progression, death or unacceptable toxicity. Complete blood test were performed before each drug administration and disease was assessed every 2 cycles.

Results: 109 pts were enrolled with the following characteristics: median age: 61 yrs, gastric site: 69.7%, cardiac: 23.8%, distal oesophagus: 6.4%, PS ECOG: 0-1, WHO grade ≥ 2(8.2%); monotherapy : 12.9%, combination therapy: 87.1%; peritoneal metastasis: 25.3%. At 12 months, progression-free survival rate was 52% (95% CI: 0.32-0.71) and median survival time was 13.1 months (95% CI: 9.2-15.0). The proportion of patients achieving an ORR > 2 (HR 1.878, 95% CI: 1.3-2.7, p= 0.001) were 34.8% (≤18.2%) monotherapy, 12.9% (≤18.2%) combination therapy, 87.1% peritoneal metastasis: 41.2%. Median treatment duration was 3 mos(1-12 mos). The most frequent grade 3 AEs were: neutropenia (5.5%), asthenia (2.7%), hemorrhage (1.8%). Febrile neutropenia occurred in 0.9% of the pts. No bleeding of grade ≥ 2 was reported. There were no treatment-related deaths. ORR was 17.4%, 7.1% (1.8%). Neutropenia (grade 3) were reported in 5.5% and 2.7% of pts treated with ramucirumab monotherapy and combination therapy, respectively. Stable disease was observed in 30.2%, disease control rate (DCR) was 47.6%. With a median follow-up of 8 mos (95% CI: 6.5-9.5), median PFS was 3.0 mos (95% CI: 2.3-3.6), median OS was 7.0 mos (95% CI: 5.7-8.2). On a multivariate analysis, age ≥61 or ≥61 (HR 3.18, 95% CI: 1.8-5.6, p= 0.0001) and PS ECOG ≥2 or ≥2 (HR 1.87, 95% CI: 1.3-2.7, p= 0.001) were independent prognostic factors. Median PFS was 2 months in the monotherapy group (95% CI: 0.82-3.17) and 3 months in the combination (95% CI: 2.1-3.85, p= 0.1).

Conclusions: Ramucirumab treatment, in a ‘real life’ setting, is proven to be well tolerated in an Italian cohort of pretreated MGC pts with no new safety signals.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan

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633P Systemic inflammation is associated with the density of immune cells in the tumor microenvironment of gastric cancer

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Background: The neutrophil-lymphocyte ratio (NLR) and the prognostic nutritional index (PIN) are markers of systemic inflammation known to be useful prognostic indicators in the malignancy. However, no direct evidence has yet defined the influence of inflammation on the tumor microenvironment.

Methods: A total of 288 patients who underwent curative surgery for gastric cancer were included. Preoperative peripheral blood samples were used to analyze NLR and PIN. The optimal cut-off levels for NLR and PIN were defined using receiver operating characteristic curve analysis for survival (NLR ≥ 2.7, PIN = 47.7). The densities of specific immune cells (CD3+, CD4+, CD8+, CD56+) within the tumor microenvironment were measured in tumor microarrays by immunohistochemical analysis.

Results: There were 235 patients (81.6%) in low NLR and 53 patients (18.4%) in high NLR. Low PIN was identified in 117 patients (40.6%) and high PIN in 171 patients (59.4%). CD3+, CD4+ and CD8+ immune cell density were not associated with NLR and PIN. However, in high NLR group, CD3+ immune cell density was significantly decreased compared to low NLR group (P < 0.001). Similarly, the density of CD4+ immune cells was also significantly decreased in low PIN group compared to high PIN group (P < 0.001). High NLR and low PIN were correlated with worse overall survival in multivariate analysis (P = 0.028 and P = 0.002, respectively).

Conclusions: In summary, NLR and PIN are associated with the density of CD4+ and CD8+ immune cells in the tumor microenvironment, which leads to its prognostic values of systemic inflammation in gastric cancer.

Legal entity responsible for the study: Jin Won Kim

Funding: Seoul National University Bundang Hospital

Disclosure: All authors have declared no conflicts of interest.

634P Investing the feasibility of precision medicine in gastrointestinal cancers

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Background: Molecular characteristics of patients’ (pts) tumours can determine suitability for targeted drugs, but many variants are only seen in a small percentage of pts. Targeted next generation sequencing (NGS) can be used to screen tumours for multiple variants and therefore facilitate precision medicine, but details are lacking on the practicality of this approach.

Methods: The FORMAT study (ClinicalTrials.gov identifier NCT02112357) is a single-centre study in pts with advanced GI cancer. The study aimed to investigate the feasibility of delivering NGS results (to accredited standards) in a clinically meaningful timeframe and how this could be adopted into routine clinical practice in the United Kingdom’s National Health Service (NHS). Targeted capture sequencing (mainly using archival formalin fixed paraffin embedded samples from referring hospitals) was performed to detect mutations, copy number variations and translocations in 46 genes which had prognostic/predictive significance or were targets in current/future clinical trials.

Results: Between February 2014 – November 2015, 222 pts were recruited and samples obtained for 215 pts. Of these 215 pts, NGS results for ≥ 16 of the 46 genes were obtained for 125 pts (58%) and for ≥ 2 genes in 136 pts (63%). Potentially actionable variants were detected in 90 pts (NGS success rates (results for ≥ 2 genes) improved during the study (1st pt cohort vs last pt cohort: 52% vs 65%). The proportion of successfully sequenced samples was influenced by sample characteristics, e.g. tumour cellularity (high vs low 78% vs 13%, p < 0.001), tumour content (high vs low 79% vs 27%, p < 0.001), type of sample (resection vs biopsy: 82% vs 48%, p < 0.001).

Turnaround times improved over the duration of the study, but the median time from date of study registration to date of NGS results was 19 weeks (including a median of 5 weeks for sample retrieval and 5 weeks for NGS).

Conclusions: NGS was not successfully performed in 44% of patients recruited to this study because of unavailable/inadequate tissue samples. In order for NGS to become feasible within a routine NHS setting, pathways for tissue collection and processing need to be optimised so that results can be obtained in a clinically useful timeframe.

Clinical trial identification: ClinicalTrials.gov NCT02112357; Protocol V4.0, dated 10.04.15

Legal entity responsible for the study: The Royal Marsden NHS Foundation Trust

Funding: National Institute for Health Research Royal Marsden/Institute of Cancer Research Biomedical Research Centre The Moodie Report Foundation The Clive and Ann Smith Fellowship

Disclosure: All authors have declared no conflicts of interest.
Background: American phase I studies have reported that the recommended dose of TAS-102 (trifluridine/tipiracil) was 25 mg/m² bid, although this schedule did not provide clinically relevant improvements in a phase II study of advanced gastric cancer (AGC). However, a pivotal phase III study revealed that TAS-102 at 35 mg/m² bid provided a clinically relevant improvement in overall survival among patients with metastatic colorectal cancer. Thus, we re-evaluated the efficacy, safety, and pharmacokinetic (PK) parameters of TAS-102 at 35 mg/m² bid in patients with AGC. In an expanded cohort, we also evaluated the safety and PK parameters of a 40 mg/m² bid schedule.

Methods: All patients had undergone one or two previous chemotherapy regimens that contained fluoropyrimidine, platinum agents, and taxanes or irinotecan. In this study, we assessed the investigator-determined and the independent central review disease control rate (DCR), response rate, progression-free survival (PFS), overall survival (OS), safety profiles, and PK profiles.

Results: Twenty-nine patients were assessable after completing the 35 mg/m² bid schedule. The investigator-determined DCR was 66.5% (95% CI, 47.7–82.1%) and the independent central review DCR was 51.9% (n = 27, 95% CI, 31.9–71.3%). The median PFS and OS were 2.7 months (95% CI, 1.1–3.5 months) and 14.9 months (95% CI, 7.7–14.9 months), respectively. The grade 3/4 adverse events included neutropenia (69.0%), leukopenia (41.4%), anemia (20.7%), and anorexia (10.3%). No AGC-specific toxicities were detected. In the expanded cohort, the average of PK parameters dose-dependently increased for 6 patients treated with the 40 mg/m² bid dosage. Although slightly higher grade 3–4 neutropenia (83.3%) and leukopenia (66.7%) were observed, the investigator-determined DCR was 50.0% (SD: 3; PD: 3) and no partial response cases were observed.

Conclusions: The 35 mg/m² bid dose of TAS-102 provided positive efficacy and an acceptable toxicity profile in patients with AGC. A randomized, double-blind, placebo-controlled, phase III study is ongoing to validate these findings.

Clinical trial identification: UMIN000007421
Legal entity responsible for the study: Exploratory Oncology Research & Clinical Trial Center, National Cancer Center Funding: The Renovation Project of Early and Exploratory Clinical Trial Center, National Cancer Center Research and Development Fund (24-A-1)Disclosure: K. Muromoto, S. Nomura: Japan Breast Cancer Research Group (JBCRG). S. Takahashi: Research funding: Taiho Pharmaceutical Company. K. Nishikawa, T. Yoshikawa, K. Fujitani, K. Tanabe, S. Ito: Corporate-sponsored Research: Taiho, Boehringer-Ingelheim, Novartis, Bayer. All other authors have declared no conflicts of interest.

Abstracts
Topo1 (rho = 0.310, P = 0.031), and APTX (rho = 0.561, P < 0.001). Correlations were also observed between the mRNA expression of plasma/tumor BRCA1 levels and doctaxel sensitivity (P < 0.001), plasma/tumor TS and pemetrexed sensitivity (P < 0.001), plasma/tumor BRCA1 and platinum sensitivity (P = 0.016, tumor, P < 0.001), and plasma/tumor Topo1 and trastuzane sensitivity (P = 0.015, tumor, P = 0.011). Among another 64 patients with advanced cancer (Stage IV), 55 patients were in the test group receiving chemotherapy according to plasma gene detection, and 9 patients were in the control. The median overall survival of test group was 15.5 months (95% CI = 10.1 to 20.9 months), the progress free survival was 9.1 months (95% CI = 8.0 to 10.2 months), which were significant longer than the control (P = 0.047 for OS, P = 0.036 for PFS). The risk of mortality was higher in the control than patients treated according to the plasma gene detection (HR in the control = 2.34, 95% CI = 0.93 to 5.88, P = 0.071).

Conclusions: Plasma mRNA expression level mirror those in the tumor and can be used as promising predictive biomarkers to predict chemo-efficacy.

Legal entity responsible for the study: The Comprehensive Cancer Centre of Drum Tower Hospital

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A randomized phase II study of leucovorin, 5-fluorouracil with or without oxaliplatin (LV5FU2 vs. FOLFOX) for curatively-resected, node-positive esophageal squamous cell carcinoma

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Background: Optimal perioperative treatment for resectable esophageal squamous cell carcinoma remains investigational. In this study, we evaluated the efficacy and safety of leucovorin and 5-fluorouracil (LV5FU2) and LV5FU2 plus oxaliplatin (FOLFOX) combination chemotherapy given as adjuvant therapy for curatively-resected, node-positive esophageal squamous cell carcinoma.

Methods: Patients with pathological node-positive esophageal cancer after curative R0 resection were enrolled in a Fleming’s single-stage Phase II design. Patients were randomly assigned to receive LV5FU2 (leucovorin 200 mg/m2 and 5-FU 400 mg/m2 intravenously on day 1, followed by a 46-h infusion of 5-FU 2,400 mg/m2) or FOLFOX (oxaliplatin 85mg/m2 as 2-h infusion on day 1 plus LV5FU2). Patients received either LV5FU2 or FOLFOX biweekly up to 8 cycles except disease progression or unacceptable toxicity. The primary endpoint was disease-free survival (DFS) and secondary endpoints included overall survival (OS), safety and quality of life assessments.

Results: Between Jan 2011 and Mar 2015, 66 patients were randomized (35 in LV5FU2 arm and 31 in FOLFOX arm). The median age of all patients was 60 years (range, 31-81 years) were enrolled as the intent to treat population. The per-protocol population (XP-58, FP-62, 68.3% male). The most frequent drug related Grade 3/4 AEs were diarrhea (34%), nausea (21%), vomiting (21%), and fatigue (21%). The median PFS was 7.9 months (5.8-11.6) and the median OS was 20.8 months (14.3-24.8). Median DpR of 44% (interquartile range: 16%, 55%) The median period until DpR was 9.5 weeks. ETS 20% was associated with significantly longer OS and PFS when compared with ETS <20% (ETS ≥20% vs <20%: OS 24.4 vs 9.6 months, HR 0.21 < 0.05 PFS 11.9 vs 2.9 months, HR 0.13 < 0.05). DpR ≥44% was also associated with significantly longer OS and PFS when compared with DpR <44%. (DpR ≥44% vs <44%: OS 29.7 vs 11.5 months, HR 0.24 < 0.05 PFS 14 vs 5.2 months, HR 0.22 < 0.05) There was a weak positive correlation between DpR and clinical outcomes (OS: x = 0.35, 2 = 0.003; PFS: x = 0.40, 2 = 0.00003).

Conclusions: These results indicate the potential of both ETS and DpR as a new measure of efficacy in HPAGC patients treated with 1st-line CT. Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Capcetabine/cisplatin versus 5-fluorouracil/cisplatin in Chinese patients with advanced and metastatic gastric cancer: Re-analysis of efficacy and safety data from the ML17032 study

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Background: this study presents a re-analysis of the efficacy and safety data from the ML17032 trial to confirm the non-inferiority and test the potential superiority of a capcetabine (Xeloda®)/ cisplatin (XP) combination over a 5-fluorouracil (5-FU)/ cisplatin (FP) regimen as first-line treatment for advanced gastric cancer (AGC) in Chinese patients.

Methods: In this open label phase III trial, patients with advanced gastric cancer (Stage IIIA-IV) with or without metastases were randomized 1:1 to receive Cisplatin (80mg/m2/day IV day 1) with either Capcetabine (1000mg/m2/day PO BID, days 1-14) (XP) or 5-FU (800mg/m2/day continuous IV days 1-5) (FP) every 3 weeks. The primary objective was to confirm the non-inferiority of XP over FP for progression free survival (PFS).

Results: A total of 126 Chinese patients (XP: 62, FP: 64, 75.4% male, median age 55.5 years) were enrolled as the intent to treat population. The per-protocol population consisting of 105 patients (XP: 51, FP: 54, 64.7% male) served as the primary analysis group for establishing non-inferiority. Median PFS in the XP and FP groups was 7.2 and 4.5 months respectively. The primary endpoint efficacy of PFS was met with an adjusted hazard ratio (HR) of 0.52 (95% Confidence interval [CI]: [0.32-0.85], p = 0.006). Unadjusted HR for PFS in ITT population was 0.63 (95% CI: [0.42-0.94], p = 0.022). Among secondary efficacy endpoints OS (adjusted HR 0.61 [0.37-1.01], p = 0.053) and TTF (HR 0.54, [0.35, 0.84], p = 0.006) demonstrated a trend towards superiority of XP over FP. Drug exposure was similar among 2 groups in the safety population (XP: 58, FP: 62, 68.3% male). The most frequent drug related Grade 3/4 AEs were neutropenia (XP-20.7%, FP-17.7%) and gastrointestinal disorders (XP-19.9%).
Clinical significance of microRNA expression in patients with Epstein-Barr virus associated gastric cancer

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Background: Previous reports have shown that the expression of miRNA was involved in the development or prognosis of Epstein-Barr virus associated gastric cancer (EBVaGC). Therefore, the expression or target gene of the EBV miRNA can be useful as biomarker for EBVaGC. This study investigated the clinical significance of EBV miRNA expressions in patients with EBVaGC.

Methods: After reviewing 1318 consecutive cases of surgically resected or endoscopic submucosal dissected gastric cancers, 120 patients were identified as EBV-positive using EBV-encoded RNA in-situ hybridization. Among the 120 patients, the miRNA expression was examined in 39 tumor and 39 paired normal mucosal tissues from available formalin-fixed paraffin embedded tissues. The EBV-miRNAs expression levels for EBV-miR-BART1-5p, EBV-miR-BART4-5p, and EBV-miR-BART20-5p were determined by quantitative real-time PCR and the data were normalized relative to U6 expression. The average value of EBV-miRNA expression levels was used as the cutoff point.

Results: The median age of the patients was 64 years (40-76) and 31 (79.5%) were male. The pathologic stages after surgical resection were as follows: stage I (n = 13), stage II (n = 12), and stage III (n = 14). The expression of these miRNAs was significantly higher in tumor tissue than paired normal tissue (P < 0.001 for each). Of these 39 patients, 14 patients (35.9%), 11 patients (28.2%), and 13 patients (33.3%) were determined as BART1-5p-high expression group, BART4-5p-high expression group, and BART20-5p-high expression group, respectively. In a univariate analysis, BART20-5p were significantly associated with longer recurrence-free survival (RFS) (P = 0.028), yet not overall survival. In a multivariate analysis, BART20-5p expression level has a tendency of favorable outcome indicator for RFS (P = 0.093, HR = 0.219, 95% CI = 0.037–1.290).

Conclusions: The EBV-miR-BART1-5p, EBV-miR-BART4-5p, and EBV-miR-BART20-5p were highly expressed in EBVaGC tissues, and the expression level of EBV-miR-BART20-5p may predict RFS for patients with EBVaGC. Further studies are warranted to elucidate the roles of EBV miRNAs in carcinogenesis of EBVaGC, which would be a potential therapeutic target.

Legal entity responsible for the study: N/A

Funding: Ministry of Health & Welfare, Korea

Disclosure: All authors have declared no conflicts of interest.

Prognostic significance of neutrophil to lymphocyte ratio (NLR) in patients (pts) with resectable gastric gastroesophageal junction (GJG) adenocarcinoma undergoing peroperative chemotherapy


Legal entity responsible for the study: The Christie NHS Foundation Trust, Manchester, UK

Background: No validated prospective prognostic markers exist for pts with resectable gastric/GJG adenocarcinoma (AC). There is evidence that NLR and platelet-to-lymphocyte ratio (PLR) predict outcomes in different types of malignancies. We aimed to explore the prognostic significance of NLR in pts with resectable gastric/GJG AC undergoing peroperative chemotherapy.

Methods: In this retrospective cohort study, baseline neutrophil, lymphocyte and platelet count levels were recorded for all pts with resectable gastric/GJG AC commenced on neoadjuvant ECX-based chemotherapy. Among the 120 patients, the NLR was calculated as total neutrophil count divided by total lymphocyte count. NLR was classified into tertiles, and patients were followed until death or last follow-up.

Results: Of 368 pts included, 95 pts (26%) had gastric and 273 (74%) had GOJ AC patients. Median OS was 139 mo (95%CI = 91-187, p = 0.001). A baseline prognostic model incorporating NLR, PS and T stage was constructed. Pts with no poor prognostic features (PS 0/1, T stage 1/2, NLR ≤ 3.0) had increased OS compared to those with ≥1 poor prognostic features. Median OS for pts with 1, 2 or ≥3 poor prognostic features were 110.0 mo (95%CI = not reached), 28.0 mo (95%CI = 18.5–37.5) and 17 mo (95%CI = 9.9–24.1), respectively.

Conclusions: NLR is highly prognostic in pts with resectable gastric/GJG AC undergoing neoadjuvant ECX chemotherapy. We propose a baseline prognostic model that might inform prognosis and aid stratification of pts in clinical trials.

Legal entity responsible for the study: The Christie NHS Foundation Trust

Funding: The Christie NHS Foundation Trust

Disclosure: All authors have declared no conflicts of interest.
hypothesized that genomic LOH would be associated with survival in pts treated with EOC ± P in the REAL3 study.

**Methods:** Methods: REAL3 was a randomised, open-label phase 3 trial in pts with treatment naïve, metastatic or locally advanced oesophagogastric cancer (OGC) assessing addition of P to EOC, no survival benefit was associated with EOC + P therapy. Pre-treatment tumour biopsies were selected for high tumour content (>30%). The percentage of interrogable genome with LOH (≥LOH) was quantified by assessment of single-nucleotide polymorphisms spanning the whole genome using a next-generation sequencing based assay (Frampton et al., Nat. Biotechnol. 2013). Optimisation of survival benefit as measured by Hazard Ratio (HR), its significance, sensitivity and specificity was used to derive an EOC cut-off separating pts into LOH high and low cohorts which were associated with survival.

**Results:** Results: Eighty six (of a total 553 pts treated) tumours were sequenced (n = 42 EOC, n = 44 EOC + P). LOH was inferred for 54 (63%). Median ≥LOH for the entire cohort was 12.1%, this was highest for oesophagogastric (15.4%), median ≥LOH for stomach and oesophageal tumours were 11.4% and 11.6% respectively. Pts with LOH ≥21% (n = 9/54, 17%) appeared to have a progression free (HR 0.48 (95% CI 0.21-1.09), p = 0.08) and overall survival (HR 0.43 (95% CI 0.19-0.97), p = 0.04) benefit. The proportion of pts with oesophagogastric, OGI and stomach cancers with LOH ≥21% were 16%, 23% and 8% respectively.

**Conclusions:** Conclusions: Genomic LOH was inferred for the majority of sequenced samples. OGI tumours had the highest median LOH. An LOH high cut-off of ≥21% (17% of the population) was associated with an overall survival benefit for pts treated with platinum chemotherapy. LOH high platinum sensitive pts may benefit from PAP inhibitor therapy; we will investigate this hypothesis using rucaparib in the PLATFORM trial.

**Legal entity responsible for the study:** The Royal Marsden NHS Foundation Trust

**Funding:** Clovis Oncology

**Disclosure:** I. Chau: Advisory board: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, Celgene. All other authors have declared no conflicts of interest.

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**650P Efficacy and tolerability of first-line chemotherapy in elderly patients (age ≥70 years) with metastatic gastric cancer: a multicenter study of the Anatolian Society of Medical Oncology (ASMO)**


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**Background:** Gastric cancer is that generally diagnosed in advanced stages is the second leading cause of cancer-related death worldwide. Although chemotherapy has benefit on quality of life and overall survival (OS) in metastatic gastric cancer (MGC), OS usually remains less than a year. Here, the efficacy and tolerability of first-line chemotherapy in MGC patients aged 70 years and older was investigated.

**Methods:** As a multicenter study of ASMO, 305 patients followed in 17 centers between 2005 and 2015 were included. Patients who were 70 years and older at the time of MGC diagnosis and who had received at least two cycles of chemotherapy in the first-line setting were evaluated retrospectively.

**Results:** Results: The clinical and demographical features of the patients were presented in Table 1. Median age was 75 (min-max 70-90). Median follow-up time was 8 months (range 0.2-108). Median OS was 9 months (95% CI 5.2-6.7) and median OS was 10 months (95% CI 8.4-11.6). Partial response was achieved in 26.2% and stable disease in 16.7% of the patients. The most common chemotherapy related grade 3 hematologic toxicity was neutropenia (22%). Poor ECOG performance status, history of surgical treatment and less number of metastatic organs had statistically significant benefit on OS and OS (p < 0.05). The number of drugs in the regimens was positively correlated with both response rates of treatment and with grade 3-4 neutropenia rates (p = 0.004, p = 0.081; respectively).

**Conclusions:** We observed that first-line chemotherapy was effective and tolerable in elderly patients. The chemotherapy regimen (multiple or single) and the dose reduction at the beginning did not affect treatment response. It is reasonable to choose the minimum toxic and maximum tolerable chemotherapy regimen. It will be more relevant to use physiological age evaluations like ECOG performance status than biological age in treatment decision.

**Legal entity responsible for the study:** Anatolian Society of Medical Oncology (ASMO)

**Funding:** N/A

**Disclosure:** All authors have declared no conflicts of interest.

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**651P Nab-paclitaxel as second line treatment in advanced gastric cancer: A HORG multicenter phase II study**


Medical Oncology, Hellenic Oncology Research Group (HORG), Athens, Greece

**Background:** There are few therapeutic options for the treatment of metastatic gastric and gastroesophageal junction adencarcinomas which fail first-line chemotherapy. A phase II multicenter study of second line nab-paclitaxel was conducted aiming to evaluate its efficacy and tolerance in patients with advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma.

**Methods:** Thirty-nine patients (median age 62 years) with locally advanced inoperable and metastatic gastric and GEJ adenocarcinoma were enrolled. All patients had a PS of 0-1, 17 pts (43.6%) had prior surgery, 4 had received prior adjuvant chemotherapy, and 33 (84.6%) had received DCF in the first line setting. The median time from the prior treatment was 2.6 months (range, 1.0-13.8). Nab-paclitaxel was given weekly (125mg/m2, d1,d8, and d15 every 28 days).

**Results:** Results: Partial response (PR) was achieved in nine pts (23.1%), disease stabilization (SD) in 11 (28.2%) and disease progression in 18 (46.2%) for an ORR of 23.1% (95% CI 0.93-0.36) and a DCR of 51.3%. Responses were observed irrespectively of the prior administration docetaxel-based chemotherapy. The median progression free survival was 3.0 months (95% CI 2.1-3.8) and the median overall survival 6.8 months (95% CI 1.0-7.8). Six (15.3%) pts developed grade 3/4 neutropenia, 7 pts (18%) grade 2-3 anaemia and 8 (20.5%) grade 2-3 neurotoxicity. Other AE were mild (grade <2). There was no treatment-related death but treatment discontinuation was required in 3 (7.7%) pts due to adverse event-related reasons.

**Conclusions:** Second line nab-paclitaxel is an active and well tolerated treatment for patients with locally advanced inoperable/metastatic gastric and GEJ carcinomas even in pre-treated pts with a docetaxel-based regimen and merits further evaluation in the first-line setting.

**Table: 651P Demographic Data/Responses**

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<tr>
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<td>1</td>
</tr>
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<td>2</td>
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<td>3</td>
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<tr>
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<td>74-79</td>
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<tr>
<td>1 drug</td>
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<tr>
<td>2 drugs</td>
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<td>3 drugs</td>
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**Table: 650P**

<table>
<thead>
<tr>
<th>n</th>
<th>%</th>
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<tr>
<td>Response to treatment</td>
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<tr>
<td>CR/PR (ORR)</td>
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</tr>
<tr>
<td>SD</td>
<td>9</td>
</tr>
<tr>
<td>Disease Control Rate (DCR)</td>
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<tr>
<td>Time from prior treatment*</td>
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</tr>
<tr>
<td>Median (min-max)</td>
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</table>

**Clinical trial identification:** NCT02251951

**Legal entity responsible for the study:** N/A

**Funding:** Celgene

**Disclosure:** All authors have declared no conflicts of interest.
Differences exist between age extremes in GA patients compared to those traditionally represented in landmark trials including demographics, stage of presentation, histologic subtype, and treatment utilization. Further investigation is warranted to determine the effects of these differences on outcome.

Legal entity responsible for the study: This study is a retrospective review. No legal entities were involved in the conduct of this study.

Funding: Mount Sinai School of Medicine

Disclosure: All authors have declared no conflicts of interest.

A randomized phase II study of pancrelipase in patients with gastrectomy to assess the prevention of weight loss

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1Surgery, Kansai Rosai Hospital, Amagasaki, Japan, 2Surgery, Minoh City Hospital, Minoh, Japan

Background: Gastrectomy for gastric cancer is associated with weight loss, which could lead to deterioration of quality of life and even prognosis of patients. Pancrelipase (PL) is pharmaceutical preparation of extracted pancreatic enzyme (pancreatin) with high density from pancreas of the pig. We conducted a randomized phase II single-center study was performed, in which the effects of pancrelipase for the suppression of weight loss and the improvement of nutrition after gastrectomy were assessed.

Methods: Patients were randomly divided to receive the PL or not. The PL group received 1800mg/day for 6 months and more after surgery, starting from the day the patients took normal diets. The primary endpoint was the percentage of body weight loss (%BWL) from the presurgical weight to that 6 months after surgery. Body composition, BT-PABA (PD1) test and various blood test results were evaluated at 3, 6 and 12 months after surgery.

Results: 172 patients (distant gastrectomy in 128 patients, total gastrectomy in 44 patients) were enrolled from July 2012 through March 2015. 88 patients were PL group and 84 patients were non-PL group. The % BWL after total gastrectomy in 6 months were significantly higher than that after distal gastrectomy (15.2% vs 7.9%). The % BWL of PL group was lower than that of non-PL group, but which was not statistically significant (8.3% vs 10.6% p = 0.06). The % of reduction of the lean body mass was lower in PL group than that in non-PL group (p = 0.09), whereas the % of fat mass were not difference in two groups.

Conclusions: Administration of PL might be lessened postoperative BWT by means of keeping lean body mass. Legal entity responsible for the study: N/A

Disclosure: All authors have declared no conflicts of interest.

Conditional survival probability in patients with resected oesophageal adenocarcinoma receiving neoadjuvant chemotherapy

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Background: Traditional recurrence and survival figures are based upon factors determined at baseline and become less relevant for patients over time. Conditional

Table: 653P

<table>
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<th>VA</th>
<th>MA</th>
<th>EE</th>
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<tbody>
<tr>
<td>Sex</td>
<td>N  = 118,417</td>
<td>Male/Female</td>
<td>52.8%/47.2%</td>
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<tr>
<td>Race</td>
<td>N  = 113,572</td>
<td>White/Black/Asian</td>
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<td>Stage</td>
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<td>16.0%/10.5%/22.9%/52.6%</td>
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<td>Grade</td>
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<td>Surgery</td>
<td>25.7%/21.5%</td>
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<td>28.2%/21.8%</td>
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survival (CS) estimates future prognosis based upon survival to a specific time point since treatment. We analysed CS and conditional recurrence-free survival (CRFS) data for patients in the United Kingdom undergoing surgery and neoadjuvant chemotherapy for gastro-oesophageal junction (GOJ) or oesophageal adenocarcinoma (OAC).

Methods: 178 patients with GOJ/OAC treated with neoadjuvant chemotherapy and surgical resection from 2003–2012 were identified. Clinicopathological and survival data was collected as part of the Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) consortium. A multivariable parametric survival model was used to analyse factors associated with overall survival and recurrence from time of surgery.

Results: The cohort includes 305 males (80.7%) with median age 65 (range 28-83) years. 5-year RFS conditional on recurrence-free years to date increased over time (see Table). For those with stage T3/4, moderately-poorly differentiated tumours with lymphovascular invasion, 5-year disease-specific survival (DSS) improved from 77% for those with node-positive, R1 disease to 45.4% conditional on 3 years post-treatment survival; compared with 55.6% actuarial 5-year DSS increasing to 86.7% conditional on 3 years post treatment survival for patients with NO R0 disease. Age, sex, year of surgery, and Stiewert classification had no association with recurrence or mortality rate.

Table 655P Recurrence-free survival (RFS) by prognostic factors

<table>
<thead>
<tr>
<th>Poor Prognostic factor</th>
<th>T-stage</th>
<th>Nodal stage</th>
<th>Margins involved</th>
<th>5-year RFS (%) on 1 year (%)</th>
<th>5-year RFS conditional on 2 years (%)</th>
<th>5-year RFS conditional on 3 years (%)</th>
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<tr>
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<td>0</td>
<td>27.0</td>
<td>37.7</td>
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</table>

Conclusions: CSF and CS provide a more dynamic estimation of future recurrence risk and survival among patients who have accrued survival time, especially in patients with high-risk features, including positive resection margins. Margin and node positivity govern early relapse events but as the time from surgery increases these factors become less relevant.

Legal entity responsible for the study: Queen’s University Belfast

Disclosure: All authors have declared no conflicts of interest.

658P

Results of a prospective, multicenter, non-interventional trial to analyze disease- and treatment-related effects on the functionality of patients with gastrointestinal tumors ≥ 75 years

J. Hofmann1, N. Härte1, J. Hofmann1, M. Neugebauer1, A. Berger2, S. Zschätzch2, T. Seidenbusch1, J. Belge1, E. Belle1, R. Jesenofsky1, N. Schulte1, U. Wieding1, M. Ebert1, J. Chi-Kern1

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Background: Cancer is a disease of the elderly (average age of onset ≥69yrs). However, there is few data available on treatment- and disease-related interactions with the elderly. We performed the analysis based on data from 2 patient cohorts (C1: ctx <2wks, n = 15; C2: ctx >8 wks, n = 15).

Methods: Prospective, multicenter non-interventional trial at two university hospitals in Germany. Included were pts ≥75 yrs (n = 30) with gastrointestinal tumors receiving chemotherapy “ctx” in the period Q1/2015 - Q1/2016. To objectify the functionality of these pts sequential geriatric assessments (G8-Questionnaire, ECOG, IADL, ADL) were performed. The analysis is based on data from 2 patient cohorts (C1: ctx <2wks, n = 15; C2: ctx >8 wks, n = 15).

Results: An initial dose reduction tended to stabilize the ADL/IADL of pts with newly initiated ctx (C1) when compared to those pts who received a 100% dosage initially (p = 0.0996). Less ≥2 toxicities (tox) were detected after initial dose reduction (p = ns). However, at the time of the analysis the tox did not correlate with a deterioration in the IADL or ADL. Pts who started ctx with a pathological G8-Screening (<14 points) functionally improved over the period of the analysis (p = ns). The disease control rate (PR + SD) had a sign impact on the functionality of these pts (ADL: p = 0.1915). In contrast, for pts receiving ctx > 8 wks (C2), a continued 100% dosage did not result in a deterioration in the ADL/IADL (additionally no correlation between tox and the IADL/ADL has been detected). C2 pts with an initial G8 < 14 showed no further improvement, however pts with a G8-score ≥14 tended to reach a better functional performance over time (IADL/ADL: p = 0.0048). Furthermore for C2 pts disease control (PR + SD) was also significantly associated with a functional improvement (GH/ECOG: p = 0.0013; ADL: p = 0.0026).

Conclusions: These data suggest, that dose-escalating strategies maintain the functional reserve of pts ≥75yrs with gastrointestinal tumors. However disease control was the strongest predictor for stabilized functionality.

Legal entity responsible for the study: N/A

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657P

Esophageal adenocarcinoma: Impact of a large hiatal hernia on outcomes after surgery

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Background: Hiatal hernia (HH) is a risk factor for esophageal and junctional adenocarcinoma (EGJA). Its impact on the outcomes after EGJA surgery is unknown. Objectives were to evaluate complete tumor resection rate (primary objective), 30-day postoperative outcomes and survival (secondary objectives) in patients with a HH ≥5 cm (HH group) compared to those who did not have a HH or presented with a HH <5 cm (control group).

Methods: Among 867 patients who underwent surgery for EGJA, a HH was searched for on CT scan and barium swallow, with comparison between the HH (n = 42) and control (n = 325) groups.

Results: In the HH group, EGJAs exhibited higher rates of pN3 stages (28.5% vs. 10.1%, P = 0.002), of incomplete resection (50.0% vs. 4.0%, P < 0.002) and lower mortality was significantly higher in patients who received neoadjuvant radiotherapy (20.0% vs. 0%, P = 0.040), which was related to greater cardiac and pulmonary toxicity. Conclusions: For the first time, we showed that a HH ≥5cm is associated with a poor prognosis in patients who had surgery for EGJA, linked to greater incomplete resection and lymph node involvement. Neoadjuvant radiotherapy was associated with a significant toxicity in patients with a HH ≥5cm.

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Disclosure: All authors have declared no conflicts of interest.

660P

"Many ways to skin gastric cancer" - Robotic versus laparoscopic versus open gastrectomy

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Background: Robotic surgery has gained acceptance in oncological surgery. Its relevance in gastric cancer surgery is being examined. The study presents preliminary comparison of operative and postoperative outcome between robotic, laparoscopic and open gastrectomies for gastric adenocarcinoma.

Methods: Retrospective cohort of 85 consecutive patients that underwent total or partial gastrectomy for gastric adenocarcinoma at Rambam Hospital during 2012-2015. For each patient data was collected on basic demographic characteristics, BMI, operating room time(ORT), number of dissected lymph nodes(LN), length of hospitalization(LOH), intra and postoperative complications. Non parametric statistical tests MW and Kruskal-Wallis were used for group comparisons.

Results: Study population included 55 patients after total gastrectomies, 10 of them robotic and 30 partial gastrectomies, 12 of them robotic. Age, gender and BMI were similar between patients who underwent robotic, laparoscopic and open procedures. Differences in LOH between the 3 groups were observed among patients who underwent partial gastrectomy, the difference was 64 min in total gastrectomy group and 145 min in partial gastrectomy group (p < 0.001 for both differences), but the difference in ORT between laparoscopic and robotic procedures was smaller and non-significant. The number of dissected LN was similar between the 3 procedures in total gastrectomies. In partial gastrectomies, the number of dissected
Background: PIK3CA mutations are frequently observed in gastric cancer (GC). However, their pathologic and clinical implications have not been well understood yet. Methods: Clinical and pathological data of patients with stage I-IV GC who underwent gastrectomy between May 2003 and December 2005 were retrospectively analyzed according to their PIK3CA mutation status using real-time polymerase chain reaction. Results: A total of 302 patients (male, 202) were included and the median age of patients was 63 years (range, 29-89). PIK3CA mutations were detected in 40 patients (13%). Compared with PIK3CA wild-type tumors, cytoplasmic expression of Akt was significantly increased in PIK3CA mutant tumors (immunohistochemistry 3+ vs. 17% (mutant) vs. 2% (wild type); p = 0.001). PIK3CA mutant tumors were more likely to be located in the upper third of stomach (37% vs. 18%; p = 0.021) and presented with more advanced T stage (T4; 53% vs. 33%; p = 0.018). PIK3CA mutant tumors were significantly associated with poorly differentiated histology (73% vs. 46%; p = 0.018), and increased lymphatic (93% vs. 75%; p = 0.015), vascular (33% vs. 0.005) microinvasion (73% vs. 54%; p = 0.026). In addition, these tumors exhibited significantly more lymphocyte and neutrophil infiltration in stroma (p < 0.001), and worse survival correlates related to Epstein-Barr virus positive (83% vs. 6% p < 0.001) and microsatellite instability (20% vs. 7%; p = 0.015). Nevertheless, overall survival was similar between PIK3CA mutant and wild-type patients (p = 0.944). Conclusions: PIK3CA mutations up-regulate Akt expression and confer aggressive tumor biology in GC. These data suggest that PIK3CA-mutated GC may be associated with oncologically adequate lymphadenectomy and faster patient recovery, and S-1 in patients with metastatic or recurrent gastric cancer.

Methods: Chemotherapy-naïve patients with pathologically proven unresectable recurrent or metastatic gastric adenocarcinoma were assessed for eligibility. Irinotecan and S-1 combination was administered for palliative chemotherapy. The study cohort comprised 106 patients, who were randomized into two groups and treated with irinotecan and S-1 combination with or without the addition of radiotherapy. Results: Fifty-five patients (median age 57 years) were enrolled. A total of 259 cycles of chemotherapy were administered (median of eight, range 1–23 cycles). Toxicities were evaluated in 41 patients, and the responses were evaluated in 32 patients. Major toxicities included grade 3/4 neutropenia (41.5%), febrile neutropenia (14.6%), abdominal pain (12.2%), and diarrhea (7.3%). The overall response rate was 59.4% (95% confidence interval (CI) 42.3–74.5%). The median progression-free survival and overall survival were 8.4 months (95% CI 5.3–11.5 months) and 13.1 months (95% CI 11.8–14.5 months), respectively.

Conclusions: These data suggest that the oxaliplatin, irinotecan, and S-1 combination regimen is effective and relatively well tolerable, and it seems to have potential to be a reasonable therapeutic strategy in patients with unresectable gastric cancer.

Background: Efficacy of staging laparoscopy for type 4 and large type 3 gastric cancer is regarded as a useful procedure for detecting minute peritoneal metastasis, which is difficult to identify by conventional imaging modalities. However, indications for the procedure differ across reports and remain unclear. Initial type gastric cancers could be suitable candidates for SL because of the high risk of peritoneal metastasis. The present study aimed to clarify the effectiveness and limitations of SL for patients with type 4 and large type 3 gastric cancers.

Methods: We included 140 consecutive patients with cM0, type 4 or large type 3 (8cm or larger in diameter) gastric cancer who underwent SL at the Shizuoka Cancer Center from August 2008 to December 2015. Patients who received chemotherapy before the SL were excluded. We determined the detection rate of peritoneal metastasis by SL and calculated the false negative rate of SL by recruiting patients who were diagnosed as P0 at SL and underwent laparotomy within 28 days after the SL.

Results: The detection rate of peritoneal metastasis was found in 33.6% of patients, and 54.3% of patients had peritoneal metastasis.

Conclusions: The oxaliplatin, irinotecan, and S-1 combination regimen is effective and relatively well tolerable, and it seems to have potential to be a reasonable therapeutic strategy in patients with unresectable gastric cancer.
patients were diagnosed as stage IV. In addition, 51 patients diagnosed as P0 at SL underwent laparotomy within 28 days after the SL. Among them, peritoneal metastasis was found in seven patients. Thus, the false negative rate was 13.7% (7/51).

Conclusions: SL is useful for detecting previously unsuspected peritoneal metastasis and for avoiding unnecessary laparotomy, although the high false negative rate cannot be ignored. Peritoneal metastasis was found in SL in approximately one third of patients with cM0, type 4 and large type 3 gastric cancers, and therefore, they are considered viable candidates for SL.

Legal entity responsible for the study: Masanori Tokunaga

Funding: Shizukuwa Cancer Center

Disclosure: All authors have declared no conflicts of interest.

Predictive biomarkers to ramucirumab in Asian metastatic gastric cancer patients: Circulating angiogenic factors of VEGFR2 and neuropilin are predictive to ramucirumab efficacy in Asian recurrent/metastatic gastric cancer patients

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Background: We conducted an exploratory study to identify potential biomarkers to predict therapeutic effect of ramucirumab in combination with paclitaxel as a second line treatment for recurrent/metastatic Korean gastric cancer (GC) patients.

Methods: We retrospectively reviewed clinical efficacy and toxicity in 79 GC patients who received ramucirumab with weekly paclitaxel in an open-label expanded access program after failure to first line chemotherapy. To find potential biomarker of ramucirumab, we investigated the association between efficacy of ramucirumab and tissue molecular characteristics (EVB, MMR, HER2, EGFR, C-MET etc.). Also, we measured circulating biomarkers (VEGF, sVEGFR2, HGF, neuropillin-1, IL-8, and PIGF) by ELISA method and before and after treatment in a subset of patients (n = 44 vs n = 4, respectively).

Results: With the median follow up of 5.3 months (range 0.5–10.5 months), the median progression free survival (PFS) was 4.1 months (95% CI, 3.3–4.9 months), and median overall survival (OS) was not reached. Of the 55 evaluable patients, the overall response rate (ORR) was 14.5% (8 partial responses), and disease control rate was 74.3%. Although there was no difference in PFS, OS or ORR according to receptor status, higher DCR was found in patients with EGFR high expression tumors (2+/3+) compared with low expression tumors (0–1+) (87.5% vs. 50%, p = 0.02). Regarding circulating biomarkers related to angiogenesis, longer PFS was seen in patients with higher level of pretreatment serum VEGFR2 (4.1 vs 2.4 months; p = 0.01) and lower level of pretreatment serum neuropilin-1 (5.3 vs 2.4 months; p = 0.01). The circulatory biomarkers were not related to toxicity. Currently, test of tissue based biomarkers are also under way.

Conclusions: Current study suggested that circulating biomarkers related to angiogenesis quantified by ELISA method may predict prolonged response to ramucirumab in the treatment of gastric cancer patients.

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Disclosure: S.Y. Rha: Consulting or advisory role in 2years: Merck & Co.Inc. Speakers’ Bureau in 2years: Novartis, Eli Lilly, Merck. All other authors have declared no conflicts of interest.

Adjuvant concurrent chemoradiotherapy(CRT) plus docetaxel-cisplatin- fluorouracil (DCF) versus CRT plus fluorouracil folinic acid (FUFA) in gastric cancer

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Background: Adjuvant chemoradiotherapy is the optimal management strategy in resectable gastric cancer. There is a debate about the efficacy of more aggressive CRT plus chemotherapy regimens in adjuvant setting. This study aimed to compare the efficacy of adjuvant CRT plus DCF versus CRT plus FUFA in stage III gastric cancer.

Methods: Patients with a diagnosis of stage III gastric cancer, treated with adjuvant therapy after curative resection were analyzed. Patients’ and disease characteristics, impacts of the regimen on median progression free survival (mPFS) and median overall survival (mOS) were analyzed retrospectively. DCF arm had been treated with 2 cycles DCF (docetaxel 75mg/m², cisplatin 75mg/m² on day 1, fluorouracil 750mg/m² for 4 days every 3 weeks followed by concurrent CRT with 2 cycles of FUFA (fluorouracil 425mg/m², folinic acid 20mg/m², 3 days) and 2 cycles of DCF. FUFA arm was treated with Macdonald regimen (1 cycle of FUFA for 5 days, followed by CRT with 2 cycles of FUFA and further 2 cycles of FUFA

Results: 140 gastric cancer patients, 94 in FUFA and 46 in DCF arms, were evaluated. Patient and disease characteristics were similar between groups. There were more renal toxicity (40% vs 7%, p < 0.001), emergency department admissions (66.7% vs 24.6%, p < 0.001), hospitalization due to toxicity (40.9% vs 25.7%, p = 0.068) in the CRT plus DCF regimen. Treatment related mortality was similar between groups (p=0.41).

Recurrences while under adjuvant therapy were 15.2% and 17.9% in DCF and FUFA regimens, respectively (p = 0.45). Median DFS was similar between groups (19.0 v 18.0 months, p = 0.79). 24 months OS were 53.2% for DCF and 51.9% for FUFA arms. There was no statistically significant difference in mOS (not reached v 24 months, p = 0.772).

Conclusions: There is no DFS or OS advantage of CRT plus DCF over CRT plus FUFA. More aggressive adjuvant therapy with CRT plus DCF is also more toxic than Macdonald regimen.

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A modified regimen of nab-paclitaxel and gemcitabine in advanced pancreatic cancer

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Background: Nab-Paclitaxel in combination with Gemcitabine has significantly improved outcomes in advanced pancreatic cancer. However, the published regimen of day 1,8 and 15 every 28 days is associated with significant toxicities and is not deliverable in a timely fashion in many patients. The objective of this study was to evaluate the activity, deliverability, and toxicity associated with the modified regimen of Nab-Paclitaxel and Gemcitabine.

Abstracts
Methods: Nab-Paclitaxel and Gemcitabine regimen was adapted and implemented at the Irish national pancreatic surgery centre. This constitutes a retrospective study. Patients had locally advanced or metastatic Pancreatic cancer, no prior chemotherapy for Pancreatic cancer and Performance Status ≤2. Treatment regimen was Nab-Paclitaxel 125mg/m2 and Gemcitabine1000mg/m2 on day 1 and every 3 weeks. Treatment protocol was delivered on time in 87% of cycles without any delay. Dose reductions occurred in 11% of cycles. Treatment was discontinued in 6% of patients.

Conclusions: The 21-day regimen of day1 and Nab-Paclitaxel and Gemcitabine demonstrated comparable efficacy to the 28 day 1,8,15 regimen and was associated with an improved toxicity profile and deliverability. It represents an active alternate treatment schedule for patients with advanced pancreatic cancer.

Legal entity responsible for the study: Mohammad Abdol Osman (1st) Author

Funding: HSE

Disclosure: All authors have declared no conflicts of interest.

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567P

Definitive concurrent chemoradiotherapy using S-1 in the treatment of elderly patients with esophageal cancer

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Background: Definitive concurrent chemoradiotherapy (CCRT) with 5-fluorouracil (5-FU) and cisplatin (CDDP) are often associated with significant incidence of toxicities in elderly patients with esophageal cancer. This retrospective study was aimed at investigating the efficacy and safety of using S-1 as mono and maintenance therapy combined with concurrent radiotherapy (RT) for elderly patients with esophageal cancer.

Methods: From January 2009 to December 2010, 68 (aged over 70 years) elderly patients were included. RT was delivered with a daily fraction of 1.8-2.0 Gy to a total radiation dose of 54.0-60.0 Gy using the three-dimensional conformal technique (3D-CRT). Preplanned concurrent S-1 (80mg/m2/day) was given on Days 1-14, every 3 weeks. After concurrent chemoradiotherapy (CCRT), maintenance S-1 was repeated up to four cycles.

Results: The median age was 76 years (range: 70-88 years), and the clinical stages were stage I (two patients), stage II (24 patients), stage III (28 patients), and stage IV (14 patients). 51.5% patients finished treatment on schedule and the median cycles of S-1 was five, of which 35 (51.5%) patients achieved complete response. The median follow-up time was 42.7 months, and the median overall survival (OS) and progression-free survival (PFS) time were 25.7 and 21.5 months, respectively. The 1- and 3-year OS and PFS rates were 70.6%, 41.8% and 68.1%, 32.9%, respectively. Grade ≥3 neutropenia and leukopenia were found in 14 and 13 patients, respectively. The most common non-hematologic toxicity was esophagitis including six and one patients with grade 3 or grade 4.

Conclusions: For elderly patients with esophageal cancer, S-1 as mono and maintenance chemotherapy in combination with RT could improve survival outcomes with tolerable toxicities. More clinical trials (like NCT03716688) are highly warranted to further clarify this issue.

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667P

Risk factors for esophageal fistula in esophageal squamous cell carcinoma invading adjacent organs (Ts4b) treated with definitive chemoradiotherapy

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Background: Standard treatment for unresectable esophageal squamous cell carcinoma (ESCC) with distant metastasis is definitive chemoradiotherapy (dCRT). The frequency of esophageal fistula (EF) is 10–12% in patients (pts) receiving dCRT for Ts4b ESCC and the prognosis for pts harboring EF is poor. However, its risk factors are still unclear. Therefore, we investigated risk factors for EF in Ts4b ESCC treated with dCRT.

Methods: We retrospectively analyzed the data of consecutive Ts4b ESCC pts who received dCRT with cisplatin plus fluorouracil (CF) at Shizuoka Cancer Center between Sep. 2004 and Apr. 2015. All data were collected from electronic medical records. EF was diagnosed by radiological or endoscopic examination, and/or clinical course. Inclusion criteria were as follows: (1) ECOG performance status (PS) 0–1; (2) histologically proven SCC; (3) clinically T4b (TNM 7th), (4) PS before dCRT, and (5) OCR ≥50 mGy. dCRT consisted of intravenous infusion of 70 mg/m2 cisplatin on days 1 and 29, continuous infusion of 700 mg/m2 fluorouracil on days 1–4 and 29–32, and concomitant radiation of 50–60 Gy (2 Gy/Fr).

Results: In total, 143 pts who met the inclusion criteria were analyzed, excluding 6 with EF due to iatrogenic intervention. With a median follow-up time of 31 months in censored cases, EF was observed in 34 pts (24%). The median time to EF was 2.5 months. Characteristics of pts who experienced EF versus those who did not were as follows: median age (range), 64 (41–75) vs. 65 (48–80) years; PS 0/1, 22/12 vs. 71/8 pts; circumferential lesion (CL), 24 vs. 52 pts; aorta invasion, 16 vs. 46 pts; trachea or bronchus invasion, 23 vs. 77 pts; HB <12.0 g/dl, 11 vs. 16 pts; and CRP ≥1.00 mg/dl, 20 vs. 40 pts. Overall survival was 7.5 vs. 21.0 months (P = 0.01). Among potential risk factors in univariate analysis (CL, HB <12.0 g/dl, and CRP ≥1.00 mg/dl), CL (hazard ratio (HR) 2.58, 95% confidence interval (CI) 1.11–5.99) and CRP (HR 2.39, 95% CI 1.00–5.64) were considered to be risk factors for EF in Ts4b ESCC treated with dCRT. A new treatment strategy may be needed for pts with such factors.

Legal entity responsible for the study: Takahiro Tsushima

Funding: Shizuoka Cancer Center

Disclosure: All authors have declared no conflicts of interest.

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695P

Metastasis in the lymph node station 8 in patients with Siewert’s type II EGJ adenocarcinoma and its effect on prognosis following radical surgery

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Background: Lymphogenic metastasis (LM) firstly develops in lymph nodes (LNs) along the antegrade lymph flow (LF) from the primary cancer site. Development of retrograde LF and metastases in LNs along that might be a more advanced stage of the LM. Siewert’s type II EGJ adenocarcinoma (AC) has a unique pattern of LM differing from that seen with gastric and esophageal carcinoma. We hypothesize that the LN station 8 is not on the antegrade LF from Siewert’s type II EGJ AC and its metastatic damage can impact negatively on the prognosis following radical surgery.

Methods: This is a retrospective study on 174 (m – 131, f – 43) consecutive patients (pts) with Siewert’s type II EGJ AC of T2 stage who had undergone radical surgery from January 2001 till December 2015 by our surgical team. 142 pts underwent extended total gastrectomy by transthoracic access. In all 142 pts the surgery was corrected by D2 plus low mediastinal LN dissection. For homogeneity of compared subgroups, only the pts who had undergone extended total gastrectomy and received adjuvant chemotherapy (103 pts) were enrolled into the study. The T stages according to 7th Edition of AJCC/UICC, guidelines of tumors were as following: T2 – 4 (3.9%), T3 – 35 (34.0%), T4a – 50 (48.5%) and T4b – 14 (13.6%). 5-year survival rates were analyzed comparatively in pts with (arm 1) and without metastases (arm 2) in LN station 8. The survival of the pts was calculated by the Kaplan-Meter method. The difference between the survival rates was assessed by means of the log-rank test. P ≤ 0.05 was considered to be statistically significant.

Results: Metastases in the LN station 8 were detected in 19 pts (2.8%) in T3 stage, 12 (24.0%) - in T4a stage and 6 (42.8%) - in T4b stage (p < 0.05). In all the pts with metastases in the LN station 8, the LNs stations 7 and 9 were damaged as well. But not in pts with metastases in the LNs stations 7 and 8 were metastases detected in LN station 8, which indirectly indicates that metastases in the latter station might be more advanced stage of LM. 5-year survival rates were 31.6% and 44.5%, respectively in arm 1 and arm 2.

Conclusions: Metastases in LN station 8 is a negative prognostic factor in Siewert’s type II EGJ AC and should be taken into account in risk factors for EF in multivariate analysis.

Legal entity responsible for the study: P.B. Bayramov

Funding: Azerbaijan Medical University

Disclosure: All authors have declared no conflicts of interest.

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707P

Impact of primary tumour resection on survival and chemotherapy tolerance in patients with metastatic oesophageogastric cancer undergoing palliative chemotherapy

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Background: The role of primary tumour resection in patients with metastatic oesophageogastric adenocarcinoma (mOGA) undergoing palliative chemotherapy (CTH) is the subject of an intense debate. We decided to analyse retrospectively the...
impact of primary tumour resection on survival and CTH tolerance in patients with mOGA undergoing palliative CTH.

Methods: Patients with mOGA who started palliative CTH between January 2010 and May 2015 were identified from the electronic database of the Department of Oncology at the University Hospital in Krakow. We performed a charts review to obtain baseline demographics, performance status, laboratory parameters, dates of progression, death and last follow-up. Patients were divided into two groups: A primary tumour resected, B primary tumour present. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method.

Results: One hundred sixty-five patients were identified: group A n = 89, group B n = 76. No significant differences in baseline characteristics were observed. Median OS was 10.5 months (95% CI 8.5-13.5) in group A vs 8.4 months (6.6-10.5) in group B (log-rank p = 0.013). Median PFS was 6.4 months (4.8-7.5) and 5.1 months (4.1-6.6), respectively (log-rank p = 0.019). There were no statistically significant differences in grade 3 or 4 chemotherapy-related adverse events between groups: anaemia (gra. A 3.5% vs gr. B 4.9%), leucopenia (11.6% vs 13.8%), neutropenia (47.7% vs 43.1%), febrile neutropenia (4.7% vs 4.3%), thrombocytopenia (1.2% vs 0.0%), vomiting (2.3% vs 1.4%), diarrhoea (5.8% vs 4.1%), anorexia (3.5% vs 4.2%), fatigue (3.5% vs 4.2%), mucositis (1.2% vs 1.4%), hand-foot syndrome (1.2% vs 0.0%), peripheral neuropathy (1.2% vs 0.0%). No statistically significant differences were observed for CTH cycle delays (gra. A 71.6% vs gr. B 68.5%; p = 0.799) and CTH dose reductions (gra. A 7.4% vs gr. B 7.0%; p = 0.811).

Conclusions: In this retrospective analysis, primary tumour resection in patients with mOGA improved OS and did not influence the tolerance of palliative CTH. Updated observed for CTH cycle delays (gra. A 71.6% vs gr. B 68.5%; p = 0.799) and CTH dose reductions (gra. A 7.4% vs gr. B 7.0%; p = 0.811).
Background: Trastuzumab, a monoclonal antibody directed against HER2, has become standard of care for metastatic HER2 overexpressing esophagogastric adenocarcinoma and is currently investigated as (neo)adjuvant treatment in esophageal adenocarcinoma (EAC). In clinical practice HER2 overexpression is usually determined on archived tumor material, from primary tumor biopsies or resection specimens. However, HER2 overexpression may change in the course of treatment or disease progression. The aim of this study was to assess the dynamics and clinical implications of HER2 expression in both curative and palliative setting.

Methods: Matched biopsies and resection specimens of 108 EAC patients treated with neoadjuvant chemoradiation, and 68 EAC resection specimens and matched biopsies of metachronous distant metastases were collected. All samples and specimens were simultaneously stained for HER2 by an automated immunostainer using the anti-HER2 clone EPR12573 (clone 4B5) antibody. Discordance, either up- or down-regulated HER2 expression between biopsy and resection specimen or resection specimen and metastases, was determined using the standardized HER2 expression scoring system by Hofmann et al. (Hofmann, Stoss et al 2008).

Results: HER2 overexpression (immunohistochemistry scores 2+ and 3+) was detected in 14.8% of the pre-treatment biopsies and 14.2% of the neoadjuvantly treated resection specimens. A significant discordance between biopsy and resection specimen (p < 0.05), was observed. Discordance was detected in 3.1% of the metastatic cases, HER2 overexpression was identified in 9.2% and 7.8% of the resection specimen and metachronous distant metastases, respectively.

Conclusions: HER2 overexpression is observed in 14% of the primary EAC biopsies with significant dynamics in HER2 expression between pre-treatment biopsy and neoadjuvantly treated resection specimen. Remarkably, only 3% discordance was observed between resection specimen and metachronous distant metastases. Therefore, the assessment of HER2 expression in the metastatic setting should preferably be performed on the most recent acquired material, but HER2 determination on resection material may also be valid.

Legal entity responsible for the study: AMC.

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CPI-613 enhances FOLFIRINOX response rate in stage IV pancreatic cancer

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Background: Pancreatic cancer has a current five-year survival rates of less than 10%. Current standard treatment is combination chemotherapy with FOLFIRINOX or Gemcitabine + Abraxane. The glycolic and mitochondrial metabolism is aberrant in pancreatic cancer and translates into chemo-resistance. Inhibition of glutamine metabolism can potentially synergize with therapies that increase intracellular reactive oxygen species such as chemotherapy. The lipoate derivative CPI-613 is a first-in-class agent that targets mitochondrial metabolism. Whether this novel anti-cancer agent could enhance the efficacy of FOLFIRINOX is unknown.

Methods: This phase 1 study employed a two-stage dose-escalation schema to determine the maximum-tolerated dose (MTD) and safety of CPI-613 when used in combination with modified FOLFIRINOX in patients with metastatic pancreatic adenocarcinoma. Efficacy was assessed through response rates and estimates of progression-free survival (PFS) and overall survival (OS).

Results: The maximum-tolerated dose (MTD) was 1000 mg/m². The treatment was well tolerated, establishing that a reduced dose FOLFIRINOX combination with CPI-613 is feasible. Among the 18 patients enrolled at the MTD, there were 3 (16.6%) patients with a complete response (CR), 8 with a partial response (PR), 2 with stable disease and 4 with progressive disease. The PR + CR rate was 67% with a 95% Clopper-Pearson (exact) confidence interval of 41% to 87%. As follow-up is ongoing, estimates of PFS and OS are still immature, with current median PFS estimated as at least 186 days and median OS estimated at least 268 days to date.

Conclusions: CPI-613 is a first in class non redox active lipoate derivative being tested in phase I clinical trial in combination with FOLFIRINOX. The response rate was 67%, which is more than twice higher than FOLFIRINOX (32%). The CR rate is also higher than FOLFIRINOX. This novel combination therapy may emerge as the most effective treatment for patients with stage IV adenocarcinoma of the pancreas as response rate is commonly associated with PFS and OS. Whole Exome sequencing of tumors from exceptional responders and non-responders is underway. A randomized phase 2-3 study of FOLFIRINOX vs. FOLFIRINOX + CPI613 is scheduled to be initiated in late 2016.

Legal trial identification: NCT01830541

Legal entity responsible for the study: Wake Forest University.

Funding: Cornerstone pharmaceutical.

Disclosure: All authors have declared no conflicts of interest.
Phase 1b study of WNT inhibitor vantictumab (VAN, human monoclonal antibody) with nab-paclitaxel (Nab-P) and gemcitabine (G) in patients (pts) with previously untreated stage IV pancreatic cancer (PC)

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1Medicine/Medical Oncology, University of Colorado Cancer Center Anschutz Cancer Pavilion, Aurora, CO, USA, 2Medicine/Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, 3Oncology, Indiana University Simon Cancer Center, Indianapolis, IN, USA, 4Department of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA, 5Department of Medicine, University of Colorado Cancer Center Anschutz Cancer Pavilion, Aurora, CO, USA, 6Clinical Research, OncoMed Pharmaceuticals, Redwood, CA, USA, 7Medicine/Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, 8Department of Medical Oncology, Vandercell Ingram Cancer Institute, Nashville, TN, USA

Background: VAN is a first-in-class antibody that blocks WNT signaling by interacting with 5 Frizzled receptors (1, 2, 5, 7, 8). VAN, with Nab-P and G, was very effective in causing tumor regression in pre-derived PC xenografts. A biomarker signature was developed in these models. In Phase (P) 1a, VAN was tolerated well except for fragility fractures. Thus, serum markers of bone turnover and bone density were monitored with triggers for zoledronic acid (ZA). Target modulation was seen in tumor tissues in VAN at ≥5 mg/kg every 2 weeks (q2w).

Methods: Dose escalation began with intravenous VAN q2w with a standard 3 + 3 design and was then pursued for q4w with 6-pt cohorts (with baseline ZA, if indicated, increased monitoring and more sensitive ZA triggers). Nab-P at 125 mg/m2 and G at 1000 mg/m2 were given on Days 1, 8 and 15 of 28-day cycles. Objectives were determination of safety, maximum tolerated dose, recommended P2 dose, pharmacokinetics (PK), immunogenicity, pharmacodynamics, predictive biomarkers and efficacy.

Results: 19 pts have been treated to date, the 1st 8 pts in 2 q2w cohorts (3.5 & 7 mg/kg). After 2 Grade (G) 2 fragility fractures, 11 pts were treated with a revised safety plan in 2 q2w cohorts (3 & 8 mg/kg) without further fragility fractures. With a PK half-life of 4 days (unchanged by chemotherapy), q4w dosing allowed drug washout that correlated with less fracture risk. ZA at baseline or on-study was triggered for 9 of 11 (82%) pts. VAN-related adverse events (AEs) ≥10% were nausea, fatigue, dysgeusia, rash and constipation. Only related G ≥3 AEs were fatigue (1) and nausea (1), both G3. No dose limiting toxicities were observed. Of 15 evaluable pts, 8 (53%) had a partial response with 5 (33%) having stable disease. Median progression free survival (PFS) was 7.2 months, 95% CI [1.8, 9.2] (9/19 with PFS events).

Conclusions: VAN can be safely administered at relevant doses in combination with Nab-P and G, and efficacy.

Clinical trial identification: NCT020055315

Legal entity responsible for the study: OncoMed

Funding: OncoMed

Disclosure: W. Messersmith, C. Weekes: This clinical trial was sponsored by OncoMed, which had a contract with the University of Colorado. I am named in the contract, so I am disclosing it as "research support" even though funding went to the University of Colorado. S. Cohen: Fox-Chase Cancer Ctr received funding for this study. Dr. Cohen has done an Ad Board for Bayer. S. Shahda, B. O’Neil: The University of Indiana received funding for this trial from OncoMed. H-J. Lenzi: Advisory board and lectures for Bayer, which has partnered with OncoMed for this agent. E. Dotani: Fox-Chase Cancer Ctr received funding from OncoMed to perform this trial. C. Derening: Fox-Chase Cancer Ctr received funding for this study. Dr. Derening has done an Ad Board for Bayer. A. Kapoor, C. Zhang, F. Gattaruzzi, L. Xu, J. Dupont, P. Brachmann, S. Uttamgar: employee of OncoMed and owns OncoMed stock. R. Henner: employee of OncoMed, owns stock. A. Farooki: research support and consultant, OncoMed. J. Berlin: This clinical trial was sponsored by OncoMed, which had a contract with the Vanderbilt. I am named in the contract. The same applies to Bayer (research funding for clinical trials).

Observational study of FOLFIRINOX (FFX) for unresectable/recurrent pancreatic cancer (PC) in Japanese patients (pts) (JASPAC 06): final results

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Background: For Japanese pts, there are limited data of a small phase II trial of FFX (Ozaka, Cancer Sci 2014). In this multi-center retrospective study, we previously reported the preliminary results focusing on adverse events (AEs) of FFX (Ozaka, 2016 Gastrointestinal Cancers Symposium). In this presentation, we report updated results including efficacy.

Methods: The subjects were unresectable/recurrent PC pts who received FFX in practice during one year from 20 December 2013 and were followed until December 2015.

Results: Totally, 480 pts were registered from 27 institutions in Japan. One pt was excluded from the analysis because of no administration of CPT-11. Pts characteristics were: median age 63 years, ECOG PS 0/1/2 70/29/1%, disease status recurrent (rec)/limitations of first-line chemotherapy, including efficacy.

Clinical trial identification: UMIN000014658

Legal entity responsible for the study: N/A

Funding: Yakult Honsha Co.,Ltd., and Daiichi Sankyo Co., Ltd.


Conclusion: Practical use of FFX for Japanese pts was acceptable and received reasonable PC pts to show acceptable toxicities and comparable efficacy to the previous clinical trials.

Clinical trial identification: UMIN000014658

677P

678P

Gabrinox: A phase I-II of nab-paclitaxel plus gemcitabine followed by folfirinox in metastatic pancreatic adenocarcinoma
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Background: Folfirinox (FXX) and Nab-paclitaxel/Gemcitabine (AG) showed significant improvement in efficacy compared to Gemcitabine alone in metastatic pancreatic cancer (mPC). Alternating AG and FXX may overcome resistance to primary therapy and delay tumour progression. We designed a multicenter phase I-II trial with a new sequential regimen of AG followed by FXX in first-line treatment of mPC. The phase I primary objective was to determine the recommended AG and FXX doses. Primary endpoint was to determine the dose-limiting toxicities (DLTs). The phase II will assess the efficacy of the recommended doses.

Methods: AG and FXX were administered sequentially, each AG cycle followed by a FXX cycle. Dose-escalation was:

<table>
<thead>
<tr>
<th>One cycle</th>
<th>AG (mg/m²)</th>
<th>D1, D8, D15</th>
<th>FXX (mg/m²)</th>
<th>D29, D35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level</td>
<td>Nab-paclitaxel</td>
<td>Gemcitabine</td>
<td>Oxaliplatin</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>1</td>
<td>100 800 70 150</td>
<td>Leucovorin: 400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>125 1000 70 150</td>
<td>5-FU bolus: 400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>125 1000 85 180</td>
<td>5-FU infusion: 2400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chemotherapeutic agents were administered according to standard practice, except for Gemcitabine (10mg/m²/min).

Results: From September 2013 to October 2015, 33 mPC patients were included: 7, 6 and 7 patients in levels 1, 2a and 2b, respectively, and 13 in level 3. 31 patients were evaluable for tolerance (2 not evaluable at levels 1 and 2b). Patients’ characteristics at baseline were: male 54.8%, median age 61 years (42-75), ECOG PS 0 (35.5%) or 1 (64.5%). Five DLTs were reported: 1, 2 and 2 in levels 2a, 2b and 3, respectively. All DLTs were grade 4 transient, asymptomatic neutropenia with spontaneous resolution. They occurred at treatment initiation, probably due to the absence of prophylactic GCSF treatment during AG administration. There was no limiting neurotoxicity. Promising efficacy results (response and survival) will be presented at the meeting.

Conclusions: This new regimen alternating AG and FXX shows acceptable toxicity and promising efficacy results. The recommended dose (level 3) is being confirmed in a 12 patient-expansion cohort before starting the phase II accrual.

Clinical trial identification: NCT01964287

Legal entity responsible for the study: Institut régional du Cancer de Montpellier (ICM), France

Funding: This project was supported by Celgene.


Chemotherapy for patients with non-resectable pancreatic cancer with additional chemo-radiotherapy for patients with potentially resectable tumours: Final results
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Background: Locally advanced pancreatic cancer (LAPC) is often a mix of borderline and never-resectable tumours. Multimodality treatment might downstage these tumors to allow a potential radical resection, especially the borderline group. In this ongoing phase II study we examined the feasibility of FOLFIRINOX with or without CRT followed by surgery for both borderline and never-resectable tumors (NCT-01397019).

Methods: Patients in performance status 0-1, with initially non-resectable stage II/III pancreatic cancer were offered FOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², 5FU 400 mg/m² 2400 mg/m² every 14 days. Every 4th series the patients were evaluated and offered CRT [50.4 Gy/27F & capcitabine] if deemed potentially resectable. Resections were performed if deemed possible by the MDT.

Results: Between August 2012 and present, 59 patients have been recruited with a median observation time of 17 months. Median age was 68 (range 38-87) years, with 40/60 stage II/III distribution. Median CA19-9 was 268 (range 1-13,432).

Three-hundred-sixty-two courses of FOLFIRINOX have been given, with a median of 6.0 per patient, with a median of 4 without dose modifications. Presently twenty-two patients have been treated with CRT. Sixteen patients have been resected, of which 8 received prior CRT. Median survival for all patients was 21.1 months (14-59) with a 1-year survival of 74% (58-85). For patients not resected the median survival was 14.1 months(10-16) for resected the median survival has not yet been reached. The FOLFRINOX was associated with adverse events similar to what is expected in metastatic patients.

Conclusions: FOLFRINOX with or without CRT in patients with LAPC shows promising efficacy in patients with both borderline and never-resectable tumors. Unmodified FOLFRINOX had acceptable toxicity, however dose reductions are often needed. CRT following initial FOLFRINOX was feasible and without unexpected toxicity.

Clinical trial identification: NCT-01397019

Legal entity responsible for the study: N/A

Funding: Danish Pancreatic Cancer Group

Disclosure: All authors have declared no conflicts of interest.

Randomized phase 2 trial of nab-paclitaxel plus gemcitabine, a capcitabine, cisplatin (PAXG regimen) in unresectable or borderline resectable pancreatic adenocarcinoma
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Background: A phase 1b trial defined the recommended phase 2 dose of nab-paclitaxel (150 mg/m²) in combination with capcitabine, gemcitabine and oxaliplatin (80, 30, and 1250 mg/m² every 2 weeks, respectively; PAXG regimen). A randomized phase 2 trial of PAXG or nab-paclitaxel-gemcitabine (AG) was performed (NCT01739222).

Methods: Chemo-naive patients with 18-75 years, pathologic diagnosis of unresectable or borderline resectable pancreatic adenocarcinoma (NCI/NCN definition), Karnofsky Performance Status ≥ 70 were eligible for the study. The primary endpoint was overall survival. The survival rate was 24% at 20% and 5% at 40%. The number of patients to enroll in each arm was 27. With ≥ 4 of 27 eligible patients resected, each regimen will be considered active.

Results: Between Apr 2014 and Feb 2016, 54 patients (table 1) were randomized at a single Institution to receive PAXG (arm A, N = 26) or AG (arm B, N = 28). Resection after 4-6 cycles of chemotherapy was performed only in initially borderline resectable patients (5 arm A; 5 R 0, N 40, arm B: 5 R 0, N 10). One arm A and 2 arm B patients were deemed resectable and are awaiting surgery. Treatment is ongoing in 4 patients. Main grade 3/4 toxicity was (A/B): neutropenia 76/57%, thrombocytopenia 5/9%, fatigue 10/26%; neuropathy 0/22%; diarrhea 5/13%; nausea 5/13%; serious adverse events 22/29%. A partial response was observed in (A/B) 30/32% and stable disease in 50/51% patients. CA19-9 decreased by > 49% in 95/98%, >99% in 36/39% patients with elevated basal value. Progression was observed in 7 arm A and 17 arm B patients: PFS-6 (A/B) was 100%/61%.
Table: 681P

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>PAXG</th>
<th>AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Male/female</td>
<td>13/13</td>
<td>hug:21</td>
</tr>
<tr>
<td>KPS 90-100</td>
<td>19 (73%)</td>
<td>24 (86%)</td>
</tr>
<tr>
<td>70-80</td>
<td>7 (27%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Age median</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>range</td>
<td>35-75</td>
<td>50-75</td>
</tr>
<tr>
<td>Unresectable</td>
<td>16 (62%)</td>
<td>13 (46%)</td>
</tr>
<tr>
<td>Borderline</td>
<td>10 (38%)</td>
<td>15 (54%)</td>
</tr>
<tr>
<td>Head</td>
<td>18 (69%)</td>
<td>20 (71%)</td>
</tr>
<tr>
<td>Biliary stent</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>CA19.9 &gt; ULN</td>
<td>22 (85%)</td>
<td>21 (75%)</td>
</tr>
<tr>
<td>median</td>
<td>290</td>
<td>278</td>
</tr>
</tbody>
</table>

Conclusions: Both AG and PAXG regimens reached the primary endpoint. Preliminary results suggest that the addition of cisplatin and cetuximab to AG backbone is feasible and seems to improve disease control. The PAXG regimen warrant further evaluation in this setting of patients.

Clinical trial identification: ClinicalTrials.gov NCT01730222

Legal entity responsible for the study: IRCCS San Raffaele, Milan, Italy

Funding: Celgene

Disclosure: M. Reni: Advisory role: Celgene, Boehringher Ingelheim, Genentech, Lilly, Merck Serono, Baxalta, Pfizer, Novocure, Halozyme. All other authors have declared no conflicts of interest.

682P

Nab-paclitaxel in substitution of oxaliplatin and irinotecan in folfoxirinox schedule as first-line therapy in patients with metastatic pancreatic cancer: results of phase I dose finding of NabucO study by GOIRC

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Background: FOLFIRINOX and nab-paclitaxel (nab-p) plus gemcitabine are effective regimens in first line treatment for metastatic pancreatic cancer (mPC). NabucO study is designed to define dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of nab-p added to FOLFIRI or FOLFOX in first line for mPC. We report final results of dose-finding for both schedules.

Methods: Patients with mPC, untreated for metastatic disease and PS ECOG 0-1 received leucovorin 400 mg/m2, 5FU 48h ci 2400 mg/m2, and irinotecan 180 mg/m2 (Arm A) or oxaliplatin 85 mg/m2 (Arm B) plus nab-p iv per cohort escalation assignment every 2 weeks for up to 12 cycles. The design was the standard 3 + 3 phase 1 dose escalation, with a nab-p dose increased by 10 mg/m2 for each cohort starting with 90 mg/m2. The MTD was established by DLTs according with Common Toxicity Criteria for Adverse Events (CTCAE). The evaluation was defined as the highest dose level at which less than 2 of 6 pts experienced a DLT during cycle I, with a confirmatory cohort expansion of at least additional 3 pts.

Results: From February 2014 to October 2015, a total of 63 pts were enrolled, 27 pts received nab-p FOLFIRI while 36 pts were treated with nab-p-FOLFOX. For Arm A median age was 62 years (range 38-75) and in Arm B was 60 years (range 38-74). DLTs during first cycle at corresponding dose level are listed in the table below.

Table: 682P

<table>
<thead>
<tr>
<th>LEVEL Nab-p mg/m2</th>
<th>DLTs with FOLFIRI</th>
<th>DLTs with FOLFOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td>Liver toxicity G3 (1/6)</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>None (MTD)</td>
</tr>
<tr>
<td>5</td>
<td>130</td>
<td>Neutropenia G4 and leucopenia G3 (1/6)</td>
</tr>
<tr>
<td>6</td>
<td>140</td>
<td>Neutropenia G4 and thrombocytopenia G3 (1/3)</td>
</tr>
</tbody>
</table>

Conclusions: According to the study plan, the MTD of nab-p with FOLFIRI is 120 mg/m2, and with FOLFOX is 160 mg/m2. The phase II study to assess efficacy of these regimen in term of overall response rate (ORR) is currently ongoing.

Clinical trial identification: EudraCT 2013-002275-18

Legal entity responsible for the study: GOIRC Gruppo Oncologico Italiano di Ricerca Clinica

Funding: Celgene

Disclosure: All authors have declared no conflicts of interest.

683P

Impact of age, bilirubin, and disease burden in unresectable pancreatic cancer patients receiving first-line chemotherapy: A population-based analysis

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Background: FOLFIRINOX (FFN), nab-paclitaxel plus gemcitabine (NG), and gemcitabine (gem) are 3 systemic therapies that provide clinically meaningful benefit to patients with unresectable pancreatic cancer (UPC). Clinical trials have previously excluded patients with advanced age, elevated bilirubin, or locally advanced disease. Our aim was to examine whether age, bilirubin, and disease extent affected treatment outcomes.

Methods: Patients diagnosed with UPC who initiated palliative chemotherapy from August 2014 to August 2015 at any of 1 of 5 cancer centers in British Columbia were identified from the provincial pharmacy. Clinical, pathological, treatment, and outcome characteristics were compared.

Results: 159 patients were included: 53% men, 78% ECOG 0/1, and 71% with metastatic disease. Patients who received FFN and NG were younger (p <0.001), in better performance status (p <0.001), and exhibited fewer metastases at presentation (p = 0.032) (Table). Bilirubin did not alter treatment selection (p = 0.502). Patients treated with FFN or NG also experienced significantly longer median overall survival (OS) when compared to those treated with gem after adjusting for confounders (11.2 vs 4.1 months, respectively; FFN: HR 0.391, 95%CI 0.192-0.796, p = 0.009, and NG: HR 0.239, 95%CI 0.132-0.430, p < 0.001). Likewise, progression-free survival (PFS) was longer among patients on FFN or NG in comparison to gem. Neither advanced age nor elevated bilirubin at presentation affected OS (p >0.05). Having metastatic instead of locally advanced disease significantly impacted OS (p <0.001), especially for those on gem (p = 0.020).

Table: 683P

<table>
<thead>
<tr>
<th>FFN</th>
<th>NG</th>
<th>Gem</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65</td>
<td>37%</td>
<td>58%</td>
<td>78%</td>
</tr>
<tr>
<td>Bilirubin &gt;18</td>
<td>19%</td>
<td>19%</td>
<td>28%</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>59%</td>
<td>78%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Conclusions: Receipt of FFN and NG portended a better prognosis than gem alone. In the absence of a randomized comparison of all 3 regimens, our population-based study revealed that the introduction of modified FFN and NG confers real world effectiveness for UPC patients regardless of age and bilirubin at presentation.

Legal entity responsible for the study: Ying Wang

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
Background: Hyperbilirubinemia is a common disease effect in patients (pts) with metastatic pancreatic cancer (mPC). As clinical trials often exclude them, data on management of these pts are rare. In the framework of a German observational multi-center study (QOxane), quality of life and therapy data are currently being collected in pts with mPC receiving a combination of nab-paclitaxel and gemcitabine. This is an interim analysis on hyperbilirubinemia management.

Methods: Pts were included to this analysis if they entered the trial with a bilirubin level ≥1.2 mg/dl and completed at least 2 cycles. Bilirubin levels were documented for up to 4 cycles and methods of hyperbilirubinemia management have been assessed. A both descriptive and exploratory analysis was performed using IBM SPSS V 23.

Results: 25 of 294 pts (8.5%) were included. Mean bilirubin level was 2.196 mg/dl (range 1.2-12.3) at baseline and dropped considerably by the 2nd cycle to 0.84 (range 0.29-3.9, p = 0.0001). Bilirubin levels decreased in 24 (96%) and increased in 1 (4%) pts upon treatment start. 18 (72%) pts started treatment with standard dosage, 7 (28%) with a reduced regime. 10 (40%) pts underwent additional intervention: either stenting (7 pts, 28%), bile duct anastomosis (3 pts, 12%), and bile duct anastomosis (3 pts, 12%). Mean bilirubin values dropped from 4.59 to 1.09 in pts with and from 1.87 to 0.68 in pts without additional intervention. Grade 3/4 toxicity was seen in 60% of pts and most common 3/4 events were anemia, nausea, vomiting and fever. Mean Bilirubin Levels

Table: 684P

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<td>add. bile duct anastomosis (n = 3)</td>
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<td>0.47</td>
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<td>p (all pts)</td>
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1 n's indicate # of pts at baseline 2 Wilcoxon test to baseline (related samples), level of significance p = 0.05

Conclusions: Data show that bilirubin levels drop considerably after start of nab-pac gem therapy. The treatment seems to be feasible, although considerable frequencies of Grade 3/4 toxicities were observed.

Clinical trial identification: Clinicaltrials.gov: NCT012691052 AIO; trial number: AIO-LQ-0124/ass

Legal entity responsible for the study: Institute of Clinical Cancer Research, Krankenhaus Nordwest gGmbH, Prof. Salah-Eddin Al-Batran, Steinenbacher Hö 2-26, 60998 Frankfurt

Funding: Celgene GmbH


Advanced pancreatic adenocarcinoma outcomes with transition from devolved to centralised cancer care in a UK regional cancer centre

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Background: Clinical trials have demonstrated modest survival and quality of life benefits for palliative chemotherapy in advanced pancreatic cancer but this is rarely translated into real-world outcomes. We hypothesised that centralisation of advanced pancreatic adenocarcinoma management could increase chemotherapy use and potentially improve survival rates. Within Merseyside and Cheshire (UK), we transitioned from devolved to centralised pancreatic cancer management between 2011-2012. We now determine the effect of such change with respect to chemotherapy use and patient outcomes.

Methods: Data were collected for all cases of advanced pancreatic adenocarcinoma reviewed through Clatterbridge Cancer Centre according to two groups, 1st Oct 2009-31st Dec 2010 (Early Group, E) or 1st Jan 2013-31st Mar 2014 (Late Group, L). Data collected included patient demographics, treatment received and date of death. Analysis of data included overall survival (OS) and 30-day chemotherapy mortality rates.

Results: Chemotherapy was received by 43% (n= 52/121) in Group E and 67% (n= 77/115) in Group L. Reduced time to start of treatment was seen in Group L compared with Group E (18 vs 28 days, p = 0.001). More patients received second-line chemotherapy in Group L versus Group E (23.4% vs 1.9%, p = 0.001). Fewer patients aged >70 were treated in Group E compared to Group L (24.3% vs 57.4%, p = 0.001). 30-day chemotherapy mortality was 25% in Group L versus 20.8% in Group E (p = 0.573). OS was significantly increased in Group L compared with Group E (5 vs 3 years).
Clinical utility of circulating tumor DNA (ctDNA) in resectable pancreatic ductal adenocarcinoma (PDAC)

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Background: There is considerable interest in investigating ctDNA as a non-invasive biomarker, with potential use in screening, detecting minimal residual disease after curative resection and monitoring treatment response or resistance. Here we present sequential ctDNA quantification in patients (pts) with resectable PDAC using a novel and highly sensitive multiplex technology to explore the clinical utility of ctDNA as a diagnostic and prognostic biomarker.

Methods: Banked plasma and tumor samples from 32 pts with resected PDAC were retrieved. Plasma samples were collected 0-28 days before, and 28-70 days after surgery. DNA was extracted using standard protocols and analyzed using the OnTarget system, which enriches for DNA molecules containing hot spot mutations prior to sequencing. A 96-plex panel that includes the most prevalent mutations in KRAS, PIK3CA and TP53 was used.

Results: 29 pts (91%) had at least 1 mutation detected by OnTarget in the tumor sample, most frequently in KRAS codon 12 (n = 26). 25 of 29 pts with a panel-detected tumor mutation had a pre-operative blood sample available, where a concordant mutation was detected in 28 pts (sensitivity 93%). There was no correlation between pre-operative ctDNA and tumor pathologic features. At median follow-up of 16.5 months, there was no difference in recurrence-free survival (RFS) between pts with and without detectable pre-operative ctDNA (p = 0.995). Of the 22 available post-operative blood samples, a concordant mutation was detected for 5 pts. RFS was significantly shorter in pts with concordant ctDNA detected after surgery (median 2.1 vs 11.6 months, p = 0.001). A discordant mutation was detected in 3 pre-operative and 3 post-operative samples, most frequently in GNAS and PIK3CA; these pts had similar median RFS as those with no detectable plasma mutation.

Conclusions: Pre-operative ctDNA has low sensitivity, suggesting limited utility in PDAC screening, and does not appear to be prognostic. RFS was significantly shorter in pts with detectable tumor-specific ctDNA post-operatively; this analysis is limited by small numbers and short follow-up. The significance of discordant plasma and tumor mutations is unknown.

Legal entity responsible for the study: Pancreas Centre BC

Funding: Pancreas Centre BC

Disclosure: All authors have declared no conflicts of interest.

Prognostic impact of KRAS mutation in metastatic (met) pancreatic cancer patients (pts)

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Background: Pancreatic adenocarcinoma is the 4th leading cause of cancer related death, with 80% of pts presenting with met disease at diagnosis and 5-year survival rates less than 10%. Activating KRAS mutations are found in more than 90% of cases and its prognostic impact is unknown. The aim of this study is to describe the frequency of KRAS mutations and correlate it with clinical outcomes in pts with met pancreatic cancer.

Methods: From January 2011 to December 2015, 92 metastatic pancreatic cancer pts were included in the molecular prescreening program of our centre. Archived tumour samples were analysed using mass spectrometry (Mass ARRAY, Sequenom, 20 cases) until June 2014 or next-generation sequencing (Ampliseq, MiSeq, 72 cases) thereafter. All demographic, treatment and survival data were extracted retrospectively from electronic medical records.

Results: Median age at diagnosis was 64 years (range 35-82). 56 pts (61%) were male, 37 pts (40%) were diagnosed with met disease, 58 pts (63%) had liver metastases. Prevalence of KRAS mutations was 89%, only 10 pts (11%) had KRAS wild-type. The most common KRAS mutation was G12D (39 pts, 47%), followed by G12V (25 pts, 30%), G12R (2 pts, 13%) and Q61H (2 patients, 2%). At 46V, G12A and G12C mutations were found in single cases. In the overall population, median survival after metastases diagnosis (SMD) was 16.1 months (95% CI 13.8-20.1). In KRAS mutated pts, median SMD was 14.5 months, while in KRAS wild type pts median SMD was not reached (HR = 5.0 [95% CI 1.2-20.7], p = 0.01). The clonality of KRAS mutations (allelic fractions adjusted for tumour purity) had no significant impact on TRD (p = 0.73). Progression-free survival (PFS) in 1st line chemotherapy was not different according to KRAS mutation status (5.3 months in KRAS mutated, 4.2 months in KRAS wild type, HR = 1.1 [95% CI 0.5-2.9], p = 0.77).

Conclusions: With highly sensitive next-generation sequencing, KRAS mutations are found in close to 90% of met pancreatic cancer pts. The absence of KRAS mutations is associated with improved outcomes in the met setting (prognostic marker), which is not explained by higher treatment benefit during 1st line chemotherapy (not a predictive marker).

Legal entity responsible for the study: Vall d’Hebron Institut d’Oncologia

Funding: Vall d’Hebron Institut d’Oncologia

Disclosure: I. Tabernero: Consultant/Advisory role: Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Merck Serono, Novartis, Roche, Sanofi, Symphogen, Takeda and Tabo. All other authors have declared no conflicts of interest.
Background: Neoadjuvant treatment strategy has been investigated for patients (pts) with borderline resectable pancreatic cancer (BRPC). Although FOLFIRINOX has been more widely used based on its success in patients with metastatic disease, there is lack of data based on the prospective randomized trial in this setting. Therefore, we performed retrospective analysis comparing the efficacy of FOLFIRINOX and gemcitabine-based regimen.

Methods: Between February 2013 and December 2014, a total of 18 patients with histologically confirmed BRPC according to the NCCN resectability criteria were treated with FOLFIRINOX. For the comparative analysis, data of all patients with BRPC (n = 18) in our previous phase 2 study of neoadjuvant gemcitabine plus capcitabine (GEM-CAP) were extracted and included in the current analysis (Lee et al., Surgery 2012;152:851-62).

Results: In pts treated with FOLFIRINOX, median age was 54 year old (range, 29-73), and 9 patients (50%) were male. There were no significant differences in baseline characteristics between FOLFIRINOX and GEM-CAP groups, except the number of chemotherapy cycles (median 6 vs 3, respectively, p = 0.02). Surgical resection was performed in 9 pts (50%) with FOLFIRINOX and in 11 pts (61%) with GEM-CAP (p = 1.00). R0 resection rates were 50% (n = 9) in each group. Progression-free survival (PFS) was significantly higher in the FOLFIRINOX group compared to GEM-CAP group (median 6.9 vs 4.2 months [95% CI 1.6-11.1]), respectively, and there was a trend toward improved overall survival (OS) in the FOLFIRINOX group (median 21.2 months [95% CI 13.5-27.3] vs 13.6 months [11.8-15.4]; p = 0.17). In the FOLFIRINOX and GEM-CAP groups, 1-year PFS rates were 62% (95% CI, 35%–88%) and 22% (95% CI, 3%–41%), respectively, and 2-year OS rates were 45% (95% CI, 20%-70%) and 28% (95% CI, 7%-49%), respectively. The trends for the improved OS in the FOLFIRINOX group were observed regardless of surgical resection.

Conclusions: FOLFIRINOX might be associated with improved efficacy outcomes compared with GEM-CAP regimen in patients with BRPC. Further validations are necessary in the randomized trials.

Legal entity responsible for the study: Asian Medical Center

Funding: Asian Medical Center

Disclosure: All authors have declared no conflicts of interest.

SN1P | Neutrophil to lymphocyte ratio is a predictor of outcome in metastatic pancreatic cancer patients (MPC) treated with nab-paclitaxel and gemcitabine

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Background: High neutrophil to lymphocyte ratio (NLR) can be a predictor of poor outcomes in various malignancies, including pancreatic cancer (PC). Based on these data, we investigated NLR as prognostic markers in MPC pts who received first-line chemotherapy with nab-paclitaxel/gemcitabine; furthermore a prognostic model using inflammatory-based scores to predict survival was planned.

Methods: We assessed 70 pts with histologically confirmed MPC who received chemotherapy with nab-paclitaxel/gemcitabine; furthermore a prognostic model using inflammatory-based scores to predict survival was planned.

Results: Based on a median follow up of 32 months, median PFS and OS were 7.0 months (95% CI, 6.2-21.7) and 12 months (95% CI, 9.9-14.9), respectively, with a 12-month OS rate of 34.3%. According to NLR values, the patients were divided into two groups. Median PFS and OS were 5 months and 7 months (p = 0.02) and 7 months and 10 months (p = 0.003) in high (NLR ≥ 5) and low (NLR < 5) group, respectively. At multivariate analysis, Karnofsky PS ≥ 80% (HR = 0.44; CI 0.2-1.2; p = 0.04), liver metastasis (HR = 0.4; CI 0.18-8.02; p = 0.01) and NLR ≥ 5 (HR = 2.7; 95% CI 1.4-5.2; p = 0.003) were predictors of poorer OS. Based on the presence of one or more independent prognostic factors, three risk categories were identified: good-risk (0 factors, 22 pts), intermediate-risk (1 factor, 39 pts) and poor-risk (≥2 factors, 9). The median OS was 22, 10 and 7 months, respectively (p = 0.0001).

Conclusions: Baseline NLR is an independent predictor of survival of patients with MPC receiving palliative chemotherapy and could be useful to develop a simple clinical score to identify a subgroup of patients with a low chance to benefit from chemotherapy.

Legal entity responsible for the study: Second University of Naples

Funding: Second University of Naples

Disclosure: All authors have declared no conflicts of interest.

SO3P | Time course of selected treatment emergent adverse events (TEAEs) in NAPOLI-1: A phase III study of nab-IRI + gemcitabine (FFX) vs FOLFIRINOX in metastatic pancreatic cancer (mPC) previously treated with gemcitabine-based therapy


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Background: Liposomal irinotecan (nal-IRI) plus 5-FU/LV is approved in the US for patients (pts) with mPC previously treated with gemcitabine-based therapy. Primary analysis from NAPOLI-1 (NCT01494506) showed a significant median survival advantage for nal-IRI + 5-FU/LV vs 5-FU/LV (6.1 vs 4.2 mm; HR 0.67; 95% CI 0.49-0.92;
Biliary Tract Cancers (BTC) are inflammatory cancers with derangement in incidence and severity thereafter. Neutropenia, diarrhea, nausea, and vomiting were during the first 6 wk of treatment, with incidence and severity generally decreasing thereafter (Table). Similarly, prevalence and severity were highest in the first 6 wk and tended to decrease over time. Similar trends were observed in the nal-IRI and 5-FU/LV arms.

Conclusions: Neutropenia, diarrhea, nausea, and vomiting first occur early during the course of treatment with nal-IRI and are associated with a greater incidence of patients that received AC than in TT. We shortlisted genes that maintained statistical significance at multivariate analysis (gene expression, tumour site, adjuvant chemotherapy (AC) and R0/1 resection). We observed correlation between high expression of cytotoxic T-lymphocyte antigen 4 (CTLA-4) in the AT and RFS (p=0.0004). Cases with low CTLA4 had reduced expression of CD80, while cases with high CTLA4 had increased CD80 expression. IHC expression of CD80 varied in TT and AT. No association was seen between AT CD80 expression and RFS. However, CD80 expression seemed to correlate with prognosis in patients that received AC (p=0.01), suggesting that activation of this pathway may promote relapse and may be a target for adjuvant treatment. Cancer of CD8 and CD10 cells did not correlate with RFS. We also derived a immuno-gene signature that could significantly discriminate relapsed cases and was an independent prognostic factor (HR 29.43, p=0.001).

Conclusions: We showed that IP is deregulated in the AT of resected BTC and correlates with relapse suggesting that deregulation of immune infiltrate in the normal tissue creates a favourable soil for cancer cell growth.

Legal entity responsible for the study: N/A

Funding: Institute of Cancer Research.

Disclosure: All authors have declared no conflicts of interest.

Table: 693P

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Background: Although low molecular weight heparin (LMWH) is preferred treatment of cancer-related venous thromboembolism (VTE), rivaroxaban is increasingly used owing to its convenience. We aimed to compare the LMWH and rivaroxaban maintenance therapy for VTE in patients with upper gastrointestinal (GI), hepatobiliary and pancreatic (HBP) cancers.

Methods: From JAN 2004 to DEC 2014, a total of 777 and 217 patients with upper GI or HBP cancer were prescribed LMWH and rivaroxaban, respectively. With exclusion of patients who had restable disease, received treatment less than 14 days only continued due to bleeding and took anticoagulation not for therapeutic purpose, 111 and 78 patients were analyzed, respectively.

Results: Most baseline characteristics were similar between the two groups (rivaroxaban vs LMWH). Except age ≥65% (51.1% vs. 28.7%, p=0.001) and ESCOG 2 (6.4% vs. 19.8%, p=0.001). The recurrent or aggregated VTEs during anticoagulation were observed at 5 (5.1%) in the rivaroxaban group and 1 (0.9%) in the LMWH group (HR 4.41, 95% CI 0.48-40.13, p=0.188). Regarding the safety, the rivaroxaban group had significantly higher incidences of total events of bleeding (17.2% vs. 18.9%, HR 2.06, 95% CI 1.7-3.65, p=0.013) and clinical relevant bleeding (29.5% vs. 13.5%, HR 1.26, 95% CI 1.13-1.44, p=0.021) after adjusting for possible confounding factors, such as age ≥65, sex, presence of a GI mucosa lesion, poor performance status, lower BMI (<18.5) and anemia.

Conclusions: Rivaroxaban had similar efficacy to LMWH for the treatment of cancer-associated VTE, but was associated with a higher rate of total bleeding and clinical relevant bleeding in patients with upper GI and HBP cancer. Further studies are needed to validate our findings.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: V. K. Kang; received research grant from Bayer, Novartis, Roche, Sanofi. All other authors have declared no conflicts of interest.
Background: Clinical trials have failed to show benefit from adding anti-EGFR antibodies to chemotherapy in the systemic treatment of biliary tract cancer with respect to progression free and overall survival, but a trend towards higher response rate. In colorectal cancer, effect of anti-EGFR therapy is restricted to patients with RA and Braf wild-type tumors. Mutation analysis of circulating DNA may be a clinically applicable method for serial analyses. The purpose of this early cancer biomarker study was to evaluate the feasibility of extended RAS and BRAF mutation analysis of cell free DNA in blood derived from patients with metastatic biliary tract cancer.

Methods: Patients with KRAS exon 2 codons 12/13 wild type metastatic biliary tract cancer and available blood samples were included. DNA was isolated from 4 ml plasma and wild and mutant types in tumor biopsy were harbored an identical mutation.

Conclusions: Extended RAS and BRAF mutation analysis in cell free DNA from blood derived from patients with metastatic biliary tract cancer was feasible. The frequency of mutations was 23.1% and equally distributed in KRAS, NRAS and BRAF. There is high frequency of mutations beyond KRAS exon 2 may explain the lacking effect of EGFR inhibition in previous studies and justify extended mutation analysis.

Legal entity responsible for the study: Lars Henrik Jensen

Funding: Lillebaelt Hospital

Disclosure: All authors have declared no conflicts of interest.

695P

Extended RAS and BRAF mutation analysis of circulating tumor DNA in patients with biliary tract cancer

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Background: Clinical trials have failed to show benefit from adding anti-EGFR antibodies to chemotherapy in the systemic treatment of biliary tract cancer with respect to progression free and overall survival, but a trend towards higher response rate. In colorectal cancer, effect of anti-EGFR therapy is restricted to patients with RA and Braf wild-type tumors. Mutation analysis of circulating DNA may be a clinically applicable method for serial analyses. The purpose of this early cancer biomarker study was to evaluate the feasibility of extended RAS and BRAF mutation analysis of cell free DNA in blood derived from patients with metastatic biliary tract cancer.

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Legal entity responsible for the study: Lars Henrik Jensen

Funding: Lillebaelt Hospital

Disclosure: All authors have declared no conflicts of interest.

695P

Phase I study of DKN-01 (D), an anti-DKK1 monoclonal antibody, in combination with gemcitabine (G) and cisplatin (C) in patients (pts) with advanced biliary cancer (ABC)


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Background: DKK1 is an inhibitor of the canonical Wnt/beta-catenin pathway and a modulator of non-canonical signaling. High tissue DKK1 expression in intraperitoneal cholangiocarcinoma (CCA) is associated with advanced stage and shorter survival. DKK1 may enhance the invasive properties of CCA, promoting lymph node metastasis by induction of MMP9 and VEGF-C. D has previously demonstrated activity in lung and esophageal cancers. This study evaluated the maximum tolerated dose (MTD), safety and efficacy of D in combination with GC in pts with ABC.

Results: A total of 32 pts were enrolled, 22 pts evaluable for safety; 4 doses at 150 mg and 18 doses at 300 mg were administered.

Conclusions: Study completion is complete. D + GC is well tolerated; safety profile of this regimen appears similar to GC alone. Preliminary data with D (300 mg) + GC alone is thus comparable to the reported activity of GC alone.

Legal entity responsible for the study: Jennifer Eads

Funding: Leap Therapeutics, Inc.


695P

High incidence of metastases detected on 18F-FDG PET-CT in patients with gall bladder cancer incidentally discovered after laparoscopic cholecystectomy

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1Department of Nuclear Medicine, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Background: Gall bladder cancer (GBC) is a relatively rare disease with clinical and imaging features similar to benign gall bladder diseases (BGBD) like gall stone disease or cholecystitis. A few of the BGBD patients who undergo laparoscopic cholecystectomy (LC) are later found to have GBC. In these patients, it is important to evaluate the extent of disease for further management. This study was conducted to
evaluate the incidence of metastases in patients referred for 18F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) following incidental discovery of GBC after LC for BGBD.

Methods: We retrospectively evaluated the data of patients referred to our department between January 2011 and December 2015 for FDG PET-CT with GBC diagnosed on histopathology (HP) after LC for BGBD. Abnormal FDG uptake on PET images corresponding to morphological abnormalities on contrast enhanced CT images was considered positive for disease. HP examination and clinical or imaging follow-up were used as the reference standard for confirmation of diagnosis.

Results: FDG PET-CT imaging was performed 1-8 (median 3.5) months after LC in 44 patients (3M, 36F) aged 30-75 (median 50.2) years. PET-CT was positive in 32/44 (72.7%) and negative in 12/44 patients (27.3%). Loco-regional disease was detected in 30/44 patients (68.2%) involving the gall bladder fossa, liver or regional lymph nodes. Metastatic seeding to the omentum, mesentery or laparoscopic port sites was found in 15 (34.1%) and distant metastasis in 5 patients (11.3%). Based on the reference standard, 28 patients had true positive scans. Findings in 4 scan-positive patients could not be confirmed; these were presumed false positive and remain on follow-up. All 12 scan-negative patients were true negative. PET-CT showed sensitivity, specificity, PPV, NPV and accuracy of 100%, 75.0%, 87.5%, 100%, and 90.9% respectively in detecting residual / recurrent disease.

Conclusions: There is high propensity for seeding metastases when GBC is discovered incidentally during LC for BGBD. FDG PET-CT has high diagnostic performance in detecting residual / recurrent disease as well as metastases in these patients.

Legal entity responsible for the study: Department of Nuclear Medicine, PGIMER, Chandigarh, India

Funding: Postgraduate Institute of Medical Education and Research, Chandigarh, India

Disclosure: All authors have declared no conflicts of interest.

700P

NAB-PAACLITAXEL as third-line therapy after failure of gemcitabine and 5-FU based combinations in advanced gall bladder cancer patients

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Background: There is no standard third-line chemotherapy after progression on two-line therapy including gemcitabine/platinum and FOLFOX-4 based chemotherapy regimens in metastatic gall bladder cancer patients. So this study was undertaken to evaluate the efficacy and safety of single agent nab-paclitaxel in this setting.

Methods: The was a single arm prospective study, patients with performance status ≤2, who progressed on two-line therapies, were enrolled from May 2012 to December 2012. Single agent nab-paclitaxel (dose 125mg/m2) was administered on Day 1, 8 and 15 in a cycle of 28 days and i.e. until progression or unacceptable toxicity. Response evaluation was done after 2 cycles of chemotherapy.

Results: A total of 24 patients were enrolled in this study. The median age of patients was 60 years (31-71 years), of which 10 (41.66%) were males and 14 (58.33%) were females. The median number of cycles could be given were 3 (0.5 – 9.6). 13 patients (54.16%) could be given more than 3 cycles of chemotherapy and only 3 patients (12.5%) could be given more than 3 cycles of chemotherapy. Disease control rate was seen in 16 (66.66%) patients, with complete response in none, partial response in 3 (12.5%), stable disease in 5 (20.83%) patients. The median progression free survival was 2.86 months (95% CI: 2.31-3.41). The main Grade 3/4 side effects seen were hematological in 33 (33.33%) (n = 8), 7 patients (29.16%) had Grade 1/2 peripheral neuropathy.

Conclusions: Nab-paclitaxel is an effective and well-tolerated agent as a third-line option in metastatic gall bladder cancer patients. Further studies are required especially in the Indian subcontinent.

Legal entity responsible for the study: Rajiv Gandhi Cancer Institute

Funding: Rajiv Gandhi Cancer Institute

Disclosure: All authors have declared no conflicts of interest.

701P

TrkB/BDNF signaling promotes EMT mediated invasiveness and is a potential therapeutic target for gallbladder cancer

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Background: Tropomyosin-related kinase B (TrkB)/brain derived neurotrophic factor (BDNF) signaling has been shown to be activated and be involved with inducing malignant phenotype in several cancers. However, the contribution of its signaling to one of refractory malignancies, gallbladder cancer (GBC), still remains unclear. This study assessed the biological function of TrkB/BDNF signaling in GBC and investigated whether it could be a new therapeutic target in GBC.

Methods: 1) Clinical experiment: 69 patients with GBC who underwent curative surgical resection were enrolled in this study. Correlation between TrkB expression and clinicopathological findings was analyzed immunohistochemically. 2) In vitro experiment: TrkB/BDNF signaling was inhibited using k252a, siRNA and shRNA, and was activated by recombinant BDNF (rBDNF). Then, whether TrkB/BDNF signaling contributes to the invasiveness was estimated by Matrigel invasion assay using TrkB expressing GBC cell lines (TGBC, Gbk15, NOZ, Tyy GK – 1, Tyy GK – 2). Epithelial Mesenchymal Transition (EMT) related protein levels were analyzed by western blotting. 3) In vivo experiment: In Xenograft mouse model, tumorigenesis and invasiveness of TrkB shRNA transfected cells (NOZ, Tyy GK –1) was analyzed.

Results: 1) Clinical results; TrkB expression was detected in 63 (91.3%) GBC specimens. TrkB expression detected in invasive front significantly correlated with T factor (p = 0.0391) and clinical staging (p = 0.0391). Overall survival in patients with high TrkB expression was significantly lower those with low expression (p = 0.0363). 2) In vitro results; Addition of shBDNF significantly increased invasiveness and k252a treatment significantly decreased invasiveness of GBC cells. TrkB and BDNF siRNA transfection significantly inhibited the invasiveness of GBC cells. siRNA transfection increased the expression of E-cadherin and decreased the expressions of vimentin, slug, snail, and twist. 3) In vivo results; Tumors from mice injected with TrkB shRNA transfected cells significantly reduced the tumorigenicity and invasiveness.

Conclusions: TrkB/BDNF signaling enhances invasiveness of GBC, and it could be a potential therapeutic target.

Legal entity responsible for the study: Department of Cancer Therapy and Research, Graduate School of Medical Sciences, Kyushu University

Funding: Department of Cancer Therapy and Research, Graduate School of Medical Sciences, Kyushu University

Disclosure: All authors have declared no conflicts of interest.

702P

Analysis of efficacy and prognostic factors for second-line chemotheraphy in gemcitabine-refractory advanced biliary tract cancer

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Background: No standard second-line chemotherapy regimen has been established for gemcitabine (GEM)-refractory advanced biliary tract cancer (aBTC). Methods: We examined the transition rate to second-line chemotherapy and its safety and efficacy in patients with aBTC who had received first-line treatment with GEM-based chemotherapy between January 2009 and December 2015 in our hospital. We also investigated prognostic factors associated with overall survival (OS) by multivariable Cox regression analysis.

Results: Forty-six (45.1%) patients received second-line chemotherapy. One patient was excluded from this study, because second-line treatment was initiated in another hospital. The median age was 68 years, and there were 25 males and 20 females. Tumor sites were; gallbladder (n = 18), extrahepatic (n = 15), intrahepatic (n = 10) bile duct and ampulla of Vater (n = 2). Performance status was 0 in 1 and 25, and 20 patients, respectively. Cancer was metastatic in 27, recurrent in 15, and locally advanced in 3. Median CA 19-9 value was 487 U/mL. Modified Glasgow prognostic score (mGPS) was 0 (n = 24), 1 (n = 10), and 2 (n = 10). First-line chemotherapy were included; GEM + cisplatin (CDDP) (n = 19), GEM + S-I (n = 14), GEM (n = 7), GEM + OTS102 (n = 4), and GEM + radiation (n = 1). Second-line chemotherapy included; S-I (n = 20), GEM + oxaliplatin (n = 6), GEM + CDDP (n = 5), GEM (n = 5), tyrosine kinase inhibitors (n = 5), GEM + S-I (n = 2), and fixed-dose GEM + S-I (n = 2). The main grade 3/4 adverse events were biliary tract infection (n = 6), neutropenia (n = 5) and anemia (n = 5). There was one treatment-related death due to biliary tract infection. Median OS was 8.3 months, and median progression-free survival was 3.0 months. Response rate was 0% and disease control rate was 58.1%. Multivariate analysis showed that CA 19-9 ≥ 500 U/mL (hazard ratio: HR 3.45, p = 0.003), mGPS ≥ 1 (HR 3.05, p = 0.005), and liver metastasis (HR 2.62, p = 0.048) were significant prognostic factors for OS.

Conclusions: Second-line chemotherapy for GEM-refractory aBTC was inadequate. Randomized controlled trials with an appropriate stratification criteria, including CA 19-9 value, mGPS and liver metastasis, are required.

Legal entity responsible for the study: Kyoto University

Funding: Kyoto University

Disclosure: J. Funuse: Personal financial interests from Taio pharmaceutical Co., Ltd, and Eli Lilly Japan. Institutional financial interests from Taio pharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.

703P

HER2/HER3 pathway in biliary tract cancers: A systematic review and meta-analysis. A novel therapeutic druggable target?

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Background: HER2 overexpression and/or amplification has been reported as predictive factor to HER2 targeted therapy in breast and gastric cancer, whereas HER3
is emerging as a potential resistance factor. The aim of this study was to perform a systematic review and meta-analysis of the HER2 and HER3 up-regulation in biliary tract cancers (BTCs).

**Methods:** An electronic search of MEDLINE, ASCO, ESMO and AACR was performed to identify studies reporting HER2 and/or HER3 membrane protein expression by immunohistochemistry (IHC) and/or gene amplification by in situ hybridisation (ISH) in BTCs.

**Results:** Out of 440 studies screened, 40 met the inclusion criteria. Globally, HER2 overexpression rate was 26.5% (95% CI, 18.9% - 34.1%). Studies were classified as "high-quality" (HQ; 27 studies) [IHC overexpression defined as presence of moderate/ strong staining] and "low-quality" (11 studies) ["any" expression was considered positive]. When HQ studies were analysed, extra-hepatic BTCs (EH-BTCs) showed a higher HER2 overexpression rate compared to intrahepatic cholangiocarcinoma (IHCC) [19.9% (95% CI, 12.8 - 27.1%)] vs. 4.8% (95% CI, 0 - 14.5%); p-value 0.0049]. HER2 amplification rate was higher in those patients selected by HER2 overexpression [57.6% (95% CI, 16.2 - 99%)] compared to "unselected" patients [17.9% (95% CI, 0.1 - 35.4%); p-value 0.0072]. HER3 overexpression (4/4 HQ studies) and amplification rates were 27.1% (95% CI, 12.8 - 41.4%); p-value 0.0072]. HER3 overexpression (4/4 HQ studies) and amplification rates were 27.9% (95% CI, 9.7 - 46.1%) and 26.5% (one study), respectively.

**Conclusions:** Up to 20% of EH-BTCs might be HER2 overexpressed, ~60% of HER2 overexpressed BTCs can be considered amplified while HER3 is overexpressed or amplified in ~25% of BTCs. These findings may be considered in future trial development.

<table>
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Legal entity responsible for the study: Istituto Europeo di Oncologia, Milano (IT)

**Funding:** "Clinical Unit Visit" ESMO fellowship

**Disclosure:** None of the authors have declared any conflict of interest.

**704P**

Utility of multidisciplinary tumor board (MTB) in the management of hepatocellular cancer (HCC)

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**Background:** MTBs are routinely used and a requirement for comprehensive cancer centers. However, the impact of MTB is not well characterized. We studied the recommendations of MTBs on the clinical outcomes of all HCC patients presented at our liver MTB, in comparison to the 2005 practice guidelines of the American Association for the Study of Liver Disease (AASLD).

**Methods:** Data were retrospectively collected for all patients with newly diagnosed HCC and presented to our liver MTB. Patients were followed up until the time of death, last known follow-up or time of transplantation. Patients were staged at baseline using the Barcelona Clinic Liver Cancer (BCLC) staging classification. Median overall survival (OS) rates were calculated using a standard Kaplan-Meier and Cox regression model with SPSS software (v.23).

**Results:** A 312 patients out of 380 were enrolled. The average age was 62.8 years with 77.9% males. Hepatitis C was the most common etiology of HCC (57.2%). In our cohort 51.5% of the HCC patients were treated according to the AASLD guidelines by 7 months (HR 0.413; 95% CI 0.25-0.69). Patients were followed up until the time of death, last known follow-up or time of transplantation. Patients were staged at baseline using the Barcelona Clinic Liver Cancer (BCLC) staging classification. Median overall survival (OS) rates were calculated using a standard Kaplan-Meier and Cox regression model with SPSS software (v.23).

**Results:** A 312 patients out of 380 were enrolled. The average age was 62.8 years with 77.9% males. Hepatitis C was the most common etiology of HCC (57.2%). In our cohort 51.5% of the MTB recommendations were adherent to the guidelines. The first line treatment suggested by the MTB and its adherence with AASLD guidelines by stage are shown in Table 1. Our data shows that adherence to AASLD guidelines was associated with significantly longer OS in BCLC A by 21 months (HR 1.59; 95% CI 1.26-2.02). On the other hand, the OS was significantly longer in BCLC D that was not treated according to the AASLD guidelines by 7 months (HR 0.413; 95% CI 0.25-0.69).

**Conclusions:** Many patients in BCLC B/C did not receive AASLD recommended treatment, and their OS were not any different.

**Table: 704P**

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<td>HR by TGR</td>
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<tr>
<td>HR by TGR in PLC, SOAR</td>
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Conclusions: In clinical practice, the adherence to published guidelines is limited and subject to the heterogeneity of the patients and their comorbidities. MTB had a positive impact on BCLC D OS. The findings in our study suggest the need to refine the current staging and guidelines for HCC, especially for BCLC B, C, and D. MTBs need to have a bigger role in facilitating clinical trial participation.

Legal entity responsible for the study: N/A

Funding: Case Medical Center

Disclosure: P. Gholami. Consultant: Bayer. All other authors have declared no conflicts of interest.

708P

Multicentric prospective study of validation of angiogenesis polymorphisms in HCC patients treated with sorafenib. INNOVATE study

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Background: Preclinical data suggested that significant HCC growth is dependent on angiogenesis. In the ALICE-2 we study patients (PT) receiving sorafenib (S) for advanced HCC. Its immunomodulatory effects should be further explored.

Methods: A post hoc exploratory analysis was carried out on 98 ARQ197-215 pts with available absolute neutrophil count and absolute lymphocyte count, and preserved liver function. The cut-off used to define a high versus low NLR was the predefined value of 3.0, which corresponds to the median value. The effect of NLR was estimated with respect to overall survival (OS) and time to progression (TTP).

Results: No association was detected between the NLR and other known prognostic factors, including portal vein thrombosis (p = 0.671). MET expression (p = 0.592), alpha-fetoprotein levels (p = 0.837), and distant metastases (p = 0.521). In univariate analysis, compared with low NLR, a high NLR was associated with a hazard ratio (HR) for OS of 1.58 (95% confidence interval: 1.01; 2.47; p = 0.046). Moreover, in multivariate analysis, the NLR and portal vein thrombosis remained independent prognostic factors for OS within the entire cohort. Median OS was 7.8 months versus 5.1 months for patients with NLR ≤ 3.0 versus NLR > 3.10, respectively (adjusted HR: 1.62, p = 0.090). In univariate analysis, compared with low NLR, high NLR was non-significantly associated with a HR for TTP of 1.42 (p = 0.122). No statistically significant interaction between treatment effect and the NLR was detected in terms of OS.

Conclusions: Baseline NLR is a readily available and inexpensive prognostic biomarker in pts with advanced/metastatic HCC who are candidate for second-line treatments. This effect is independent of other known prognostic factors.

Clinical trial identification: NCT00988741

Legal entity responsible for the study: ManRedux Clinical and Research Center

Funding: ArQule Daichi-Sankyo


Takeda. L. Rimassa: Consulting or Advisory Role - Lilly; Merck Serrono Travel Accommodations, Expenses – ArQule. All other authors have declared no conflicts of interest.

Table 705P First line treatment and Adherence to AASLD Guidelines

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<th>BCLC C</th>
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<td>Adherence to AASLD guidelines (%)</td>
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Lenalidomide as second-line therapy for advanced hepatocellular carcinoma (HCC): biomarker exploration


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Background: Lenalidomide, which has both immunomodulatory and anti-angiogenic effects, has shown efficacy as second-line treatment for advanced HCC in a Western population. We sought to confirm the findings in an Asian population and explore potential biomarkers.

Methods: Eligible patients had histological or clinical diagnosis of HCC, documented progression with or intolerance to sorafenib or other anti-angiogenic therapy. ECOG score 0 or 1, and Child class A. Patients received 25mg/day lenalidomide on days 1-21 every 4 weeks. Tumor response was assessed by RECIST 1.1 after 4 and 8 weeks of treatment and every 4 weeks thereafter. The primary endpoint was 6-month progression-free survival (PFS) rate. Early α-fetoprotein (AFP) response was defined as a > 20% decline of AFP levels from baseline within the first 4 weeks of treatment. Vascular response (VR), evaluated using dynamic contrast enhanced magnetic resonance imaging, was defined as ≥ 240% decline in Kitara after 2 weeks of treatment.

Results: Fifty-five patients (M/F: 45/10, median age 59.8 years) were enrolled. Underlying liver diseases included hepatitis B (39%), hepatitis C (18%), and alcoholism (11%). All patients had documented progression after sorafenib treatment. The response rate (RR) was 13% (6 complete and 7 partial responses, 22 durable >2 weeks stable disease), and the disease control rate (DCR) was 53%. The 6-month PFS rate was 91%. The median PFS and overall survival (OS) was 1.8 and 8.9 months, respectively. Early AFP response (17 of 40 patients, 43%) was borderline significantly associated with higher RR (29% vs 4%, p = 0.067) and significantly associated with higher DCR (76% vs. 22%, p = 0.001) and longer PFS (median, 5.4 vs 0.9 months, p = 0.020). However, patients with and without AFP response exhibited similar OS (median, 10.7 vs 8.0 months, p = 0.307). VR (14 of 44 patients, 32%) was not associated with RR (p = 0.364), DCR (p = 0.752), PFS (p = 0.706), or OS (p = 0.135). The safety profile was comparable with other lenalidomide trials.

Conclusions: Lenalidomide exhibited moderate activity as second-line therapy for advanced HCC. Its immunomodulatory effects should be further explored.

Clinical trial identification: NCT01454804

Legal entity responsible for the study: National Taiwan University Hospital

Funding: Celgene

Disclosure: All authors have declared no conflicts of interest.
A randomized, double-blind, placebo-controlled phase III study of ramucirumab versus placebo as second-line treatment in patients with hepatocellular carcinoma and elevated baseline alpha-fetoprotein following first-line sorafenib (REACH-2)

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Background: Ramucirumab (RAM) is a humanized IgG1 monoclonal antibody that inhibits VEGF-A, C and D activation of the vascular endothelial growth factor receptor 2 (VEGFR2). The Phase 3 REACH study assessed RAM versus placebo (PBO) in the treatment of patients with advanced hepatocellular carcinoma (HCC) after prior sorafenib: significant improvement in overall survival (OS) in the overall population (N = 565) was not achieved (Hazard Ratio [HR] = 0.886; 95% CI 0.717-1.046; p = 0.1391; median OS was 9.2 months for RAM and 7.6 months for PBO. However, a meaningful improvement in OS was observed in a pre-specified subgroup of patients with baseline alpha-fetoprotein (AFP) ≥400ng/mL (N = 250) (HR = 0.674; p = 0.0059; median OS was 7.8 months for RAM and 4.2 months for PBO. The safety profile of RAM in HCC patients was considered manageable.

Trial design: REACH-2 is a randomized, double-blind, placebo-controlled phase III study of RAM and best supportive care (BSC) vs placebo and BSC in patients with HCC and elevated baseline AFP following prior therapy with sorafenib. Eligible patients will be randomized 2:1 to receive RAM (8mg/kg, IV) or PBO on Day 1 of each 14-day cycle until disease progression or other discontinuation criteria. Eligible patients must have a diagnosis of HCC (tissue or tumor with classical imaging characteristics); prior sorafenib; Child-Pugh score 5 or 6. Barceons Clinical Liver Cancer Stage C or Stage B disease not amenable/refractory to locoregional therapy; AFP ≥400 ng/mL; ECOG performance status of 0 or 1. Patients with history of encephalopathy, ongoing clinically meaningful ascites, liver transplant, or hepatic locoregional therapy after sorafenib are not eligible. The primary objective is to assess OS for patients treated with RAM vs PBO. Target enrollment is 399 patients with final analysis at 318 events (20% censoring). Secondary objectives include progression-free survival, objective response rate, safety, and patient focused outcomes. Additional objectives include assessment of biomarkers relevant to angiogenesis and HCC.

Clinical trial identification: NCT02435433

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company


A phase II study of S-1 with concurrent radiotherapy for elderly esophageal cancer patients

T. Song, S. Lv
Department of Radiation Oncology, Zhejiang Provincial People’s Hospital, Hangzhou, China

Background: Concurrent chemoradiotherapy (CCRT) with 5-fluorouracil (S-Fu) and cisplatin (CDDP) are often associated with significant incidence of toxicities in elderly esophageal cancer patients. The compound drug S-1, composed of tegafur-gimeracil-oteracil has been widely used in a variety of solid tumors including esophageal cancer. Preclinical studies indicate that S-1 shows far superior anti-tumor activities than S-Fu and enhances the sensitivity of cancer cells to the effects of radiotherapy (RT).

Trial design: This trial was designed as a prospective, single center, non-randomized, phase II study. The primary end point was the response rate which was assessed according to RECIST system 3-4 weeks after the completion of CCRT. The secondary end points were survival outcomes including OS and PFS and treatment-related toxicity. The study was designed to measure an objective response rate (CR plus PR) of 85% compared with a minimal, clinically meaningful response rate of 70%. Upon employing an α = 0.05 and a β = 0.20, the target number of patients required to achieve this level of significance was 20 cases. Considering some deviation, the preplanned number of enrolled patients was set to 22 patients. OS was determined as the time between the first day of CCRT and the last follow-up or the date of death. PFS was calculated from the date of treatment initiation to the date of documented failure or the death of the patient.
date of the last follow-up for those remaining. Toxicities were evaluated according to the common toxicity criteria for adverse events version 3.0 (CTCAE v3.0). Preplanned concurrent S-1 (70mg/m²/day) was given on Days 1-14, every 3 weeks. Radiotherapy was delivered with a daily fraction of 1.8-2.0 Gy to a total radiation dose of 54.0-60.0 Gy. After CCRT, maintenance S-1 was repeated up to four cycles. Patients were regarded eligible according to the following criteria: (i) age ≥ 70 years; (ii) cytologically or histologically confirmed esophageal carcinoma; (iii) Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1; (iv) no evidence of serious organ dysfunction; (v) expectancy life ≥ 3 months; (vi) at least one measurable lesion on CT, MRI or esophageal barium exam; and (vii) no cancer treatments prior to enrollment.

Clinical trial identification: NCT02711553
Legal entity responsible for the study: Eli Lilly and Company
Funding: Eli Lilly and Company

713Tip
Cisplatin and gemcitabine plus ramucirumab or merestinib in first-line treatment for advanced or metastatic biliary tract cancer: A double-blind, randomized phase 2 trial
J.W. Vale1, N. Boussparsem2, W. Zhang3, P.A. Walgren4, A. Vogel1
1Medical Oncology, University of Manchester/The Christie NHS Foundation Trust, Manchester, UK; 2Oncology, Elis Lilly and Company, Berneus, Belgium, UK; 3Oncology, Elis Lilly and Company, Indianapolis, IN, USA; 4Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany

Background: Angiogenesis and aberrant MET signaling are implicated in the pathogenesis and progression of invasive biliary tract cancers (BTC), including adenocarcinomas of the gallbladder, intra- and extra-hepatic bile ducts, and ampulla of Vater. Study (SIBB (NCT02711553) is a phase 2, multicenter, randomized, double-blind, multi-arm study designed to evaluate the efficacy and safety of standard of care (SOC) cisplatin and gemcitabine in combination with either metronidazol (oral type II MET kinase inhibitor) or ramucirumab (human IgG1 VEGFR2 monoclonal antibody) or respective placebo for the first-line treatment of advanced or metastatic BTC.

Trial design: Patients (n = 300) with advanced or metastatic BTC meeting eligibility requirements will be randomized to IV ramucirumab 8 mg/kg, IV placebo, oral metronidazol 800 mg/day, or oral placebo in a 2:1:1:1 fashion, and stratified by primary tumor site, geographic region, and presence of metastases. In addition to the randomly assigned treatment, all patients will receive SOC 1st-line treatment with up to 8 cycles of IV cisplatin 250 mg/m² and gemcitabine 1000 mg/m² on days 1 and 8 of 21-day cycles. IV ramucirumab and placebo will be given on days 1 and 8 of each cycle, oral treatments will be taken daily. Investigational treatment or placebo may continue past 8 cycles until disease progression or a criterion for discontinuation is met. The primary study endpoint is progression-free survival (PFS), analyzed by intention-to-treat. Secondary endpoints are overall survival, objective response rate, disease control rate, safety, pharmacokinetics, immunogenicity (ramucirumab), and patient reported outcomes. An exploratory endpoint is to correlate biomarkers with safety and clinical outcome. A phase II study has been completed on the combination of gemcitabine and ramucirumab in advanced pancreatic ductal adenocarcinoma.

Clinical trial identification: NCT02711553
Legal entity responsible for the study: Eli Lilly and Company
Funding: Eli Lilly and Company
Disclosure: I.W. Valle: Eli Lilly. Honorarium A. Vogel. Dr. Vogel reports personal from Eli Lilly and Company, outside the submitted work. All other authors have declared no conflicts of interest.

713Tip
Pembrolizumab vs best supportive care for second-line advanced hepatocellular carcinoma: Randomized, phase 3 KEYNOTE-240 study
R. Finn1, S.L. Chan2, A.X. Zhu3, J. Knox4, A.L. Cheng5, A. Siegel6, O. Bautista7, P. Weissert8, M. Kudelka9
1Oncology, Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA, USA; 2Clinical Oncology, Chinese University of Hong Kong Prince of Wales Hospital, Hong Kong, China; 3Medical, Massachusetts General Hospital, Boston, MA, USA; 4Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; 5Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; 6Oncology, Clinical Research, Merck & Co, Inc., Kenilworth, NJ, USA; 7Oncology, Clinical Research, Merck & Co., Inc., Kenilworth, NJ, USA; 8Oncology, Gastroenterology and Hepatology, Kindai University, Osaka, Japan

Background: Liver cancer is the second leading cause of cancer deaths worldwide. The tyrosine kinase inhibitor sorafenib is the standard of care for first-line hepatocellular carcinoma (HCC), and there is currently no clear standard of care for second-line HCC. Because most HCC is driven by inflammation, there is a strong rationale to evaluate immunotherapy in patients with this type of cancer. The randomized, double-blind, placebo-controlled phase 3 KEYNOTE-240 study (ClinicalTrials.gov, NCT02702481) was designed to compare the efficacy and safety of pembrolizumab, an anti- PD-1 antibody, + best supportive care (BSC) versus placebo + BSC in patients with previously treated advanced HCC.

Trial design: Eligibility criteria include age ≥ 18 years, histologically or cytologically confirmed diagnosis of HCC, documented progression after stopping treatment with sorafenib or intolerance to sorafenib, and disease not amenable to a curative treatment approach (eg, transplantation, surgery, or ablation). Patients must also have measurable disease confirmed by central imaging vendor per RECIST v1.1, Child-Pugh liver score A, ECOG performance status 0-1, and predicted life expectancy >3 months. ~408 patients will be randomized: 2:1 to receive pembrolizumab 200 mg Q2W + BSC or placebo Q2W + BSC for up to 35 cycles (~2 years) or until disease progression, unacceptable toxicity, or investigator decision. Randomization will be stratified by geographic region, macrovascular invasion, and α-fetoprotein. BSC will be provided by the investigator per local treatment practices. Response will be assessed every 6 weeks per RECIST v1.1 by central imaging vendor review. Adverse events (AEs) will be assessed throughout treatment and for 30 days thereafter (90 days for serious AEs) and graded per NCI CTCAE v4.0. Primary objectives are comparison of progression-free survival per RECIST v1.1 by central imaging vendor review and overall survival between pembrolizumab and placebo.

Clinical trial identification: NCT02702401
Legal entity responsible for the study: Merck & Co, Inc.
Funding: Merck & Co, Inc.

714Tip
A multicenter phase 4 geriatric assessment directed trial to evaluate gemcitabine +/- nab-paclitaxel in elderly pancreatic cancer patients (GrantPax)
N. Härtel1, J. Chi-Kern1, J. Belgete1, S. Beitel1, N. Schulte1, M. Maenni1, U. Westphal1, M. Eberl2
11i, Med. Klinik, Universitätsklinikum Mannheim, Mannheim, Germany; 2Clinical Research, AO-Studien-gGmbH, Berlin, Germany; 3Department of Medicine II, Universitätsklinikum Jena, Jena, Germany

Background: Recent studies demonstrated that nab-paclitaxel/gemcitabine “nab/gem” is an effective 1st line regimen for metastatic pancreatic ductal adenocarcinomas (mPDAC). There is clinical evidence indicating “nab/gem” not to be feasible in mPDAC pts ≥75 yrs. However the analyzed patients lacked a geriatric assessment to properly evaluate their functional reserve. The aim of this study is to determine with a comprehensive geriatric assessment “CGA” can predict the benefit from combined nab/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.

Trial design: GrantPax is a multicenter, open label phase 4 interventional trial with stratified parallel treatment groups (n = 45 / treatment arm). The hypothesis is that individualized assessment directed treatment algorithms identify elderly pts (70 yrs), who benefit from combined nab/gem therapy. The project uses a CGA to stratify pts as GOGO, SLOWGO or FRAIL. Depending on test results pts receive chemotherapy (GOGO: nab/gem; SLOWGO gemcitabine) or best supportive care (FRAIL). After 1 cycle of chemotherapy (4 wks) a subsequent CGA and a 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’s activities of daily living (ADL) vs ADL during CGA core assessment. The expected proportion of pts with ADL decline in each treatment group is 6%. Under this assumption it shall be shown with 80% power at 1-sided significance level α of 0.05 that the proportion of pts with functional decline is less than 20% (n = 43 / group; ADL decline: n = 2 / group). Secondary endpoints are CGA 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 that realizes a CGA-driven treatment approach to individualize cancer therapy for elderly pts.

Clinical trial identification: AIO-GER-0115; EudraCT-No.: 2015-002890-40
Legal entity responsible for the study: This Abstract have not been presented until now.
Funding: Celgene Corporation
Disclosure: N. Härtel: This investigator initiated trial is funded by the Celgene Corporation. Dr. Nicolaus Härtel participated at advisory boards organized by the Celgene Corporation (presentation incl.). There are no further conflicts of interest to
Global phase 3, randomized, double-blind, placebo-controlled study evaluating PEGylated recombinant human hyaluronidase PH20 (PEGPH20) plus nab-paclitaxel and gemcitabine in patients with previously untreated, human hyaluronan (HA)-High, stage IV pancreatic ductal adenocarcinoma

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1Digestive Oncology, University Hospital Gasthuisberg, Leuven, Belgium, 2Gastrointestinal Oncology, Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA, 3Medical Oncology, Ospedale San Raffaele, Milan, Italy, 4Medical Oncology, University of Washington School of Medicine, Seattle, WA, USA, 5Medical Oncology, Gustave Roussy, Paris, France, 6Hematology-Oncology, Beth Israel Desaconess Medical Center, Boston, MA, USA, 7Medical Oncology, Cambridge Cancer Centre, Addenbrooke’s Hospital, Cambridge, UK, 8Medical Oncology, Comprehensive Cancer Center, Klinikum München, Munich, Germany, 9Hematology Oncology, UC Irvine Medical Center, Irvine, CA, USA, 10Medical Oncology, Halozyme Therapeutics, Inc, San Diego, CA, USA, 11Medical Oncology, The Johns Hopkins University Hospital, Baltimore, MD, USA

Background: Poor outcome in pancreatic ductal adenocarcinoma (PDAC) is associated partly with stromal hyaluronan (HA) accumulation, which may compromise chemotherapy access to tumors. In animal models, PEGPH20 degrades HA in tumors. Interim data from a phase 2 study showed that PEGPH20 plus chemotherapy improved efficacy over chemotherapy alone in tumors retrospectively identified to accumulate HA (“HA-High”). The objectives of this phase 3 study are to compare efficacy and safety of standard-dose nab-paclitaxel (NAB) and gemcitabine (GEM) combined with either PEGPH20 or placebo in patients with HA-High, previously untreated, Stage IV PDAC. Primary endpoints are progression-free survival (PFS) and overall survival (OS). Secondary endpoints are objective response rate, duration of response, and safety. Trial design: 420 patients ≥18 years with untreated HA-High metastatic PDAC, ECOG PS 0-1 will be randomized (stratified by geographic region: North America/Europe/Other) 2:1 to NAB 125 mg/m² + GEM 1000 mg/m² + PEGPH20 3.0 µg/kg or to placebo. Patients with HA-High tumors will be prospectively identified by a companion diagnostic test and scoring algorithm (Ventana Medical Systems, Inc.), which defines HA-High staining in the extracellular matrix as ≥50% of the tumor surface. Treatment will be provided in 4-week cycles (Wk 1-3, Wk 4 rest) until disease progression, unacceptable toxicity, death, or consent withdrawal. PEGPH20 or placebo will be given twice weekly (Cycle 1) then weekly (Cycles 2+). NAB + GEM once weekly for all cycles. Dexamethasone will be given before and after PEGPH20 to reduce, treatment-related musculoskeletal symptoms and enosaparin will be given to minimize thromboembolic events. Tumor response will be assessed by an independent central reader by RECIST v1.1. Adverse events will be graded per NCI CTCAE v4.0. An independent Data Monitoring Committee will evaluate safety and interim data for PFS and OS analyzed by an independent statistical analysis center. Clinical trial identification: EudraCT 2015-004068-13; NCT02713804

Legal entity responsible for the study: Halozyme Therapeutics

Funding: Halozyme Therapeutics


Pembrolizumab in patients with previously treated advanced hepatocellular carcinoma: Phase 2 KEYNOTE-224 study

A. Zhu1, J. Knox2, M. Kudo3, S. Chari4, R. Finn5, A. Siegel6, J. Ma7, P.A. Watson8, A-L. Cheng9

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Background: Liver cancer is the second leading cause of cancer deaths worldwide. The tyrosine kinase inhibitor sorafenib is the standard of care for first-line hepatocellular carcinoma (HCC), and there is currently no clear standard of care for second-line HCC. Because most HCC is driven by inflammation, there is a strong rationale to evaluate immunotherapy in patients with this type of cancer. The single-arm, multisite, phase 2 KEYNOTE-224 study (ClinicalTrials.gov, NCT02702414) was designed to evaluate the efficacy and safety of the anti-PD-1 antibody pembrolizumab in patients with previously treated advanced HCC.

Trial design: Approximately 100 patients will be enrolled. Inclusion criteria include age ≥18 years, histologically or cytologically confirmed diagnosis of HCC, documented objective radiographic progression after stopping treatment with sorafenib or intolerance to sorafenib, and disease not amenable to a curative treatment approach (eg, transplantation, surgery, or ablation). Patients must also have measurable disease confirmed by central imaging vendor per RECIST v1.1, Child-Pugh liver score A, ECOG performance status 0-1, and predicted life expectancy >3 months. Patients will be allocated to receive pembrolizumab 200 mg IV Q3W for up to 35 cycles (~2 years) or until disease progression, unacceptable toxicity, or investigator decision. Response will be assessed every 9 weeks per RECIST v1.1 by central imaging vendor review. Adverse events (AEs) will be assessed throughout treatment and for 30 days thereafter (90 days for serious AEs) and graded per NCI CTCAE v4.0. The primary end point is objective response rate per RECIST v1.1 by central imaging vendor review. Secondary end points are duration of response, disease control rate, time to progression, and progression-free survival per RECIST v1.1 by central imaging vendor review; overall survival; and safety and tolerability. Clinical trial identification: NCT02702414

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: M. Kudo: Lecture fee from Bayer Co.S. Chan: Advisory Board Member: Novartis, Merck Corporate-Sponsored research: Novartis, Celgene, Eli Lilly, SIETG, AB Science, Merck, Medimmune. R. Finn: Consultant: Pfizer, Merck, Bayer, Novartis, Bristol Meyers Squibb.A. Siegel: Employee, stockholder Merck & Co., Inc.P.A. Watson: Employee and Stockholder: Merck & Co., Inc. All other authors have declared no conflicts of interest.
## Metastasis free survival (MFS) is a surrogate for overall survival (OS) in localized prostate cancer (CaP)

W. Xi, 1 C. Sweeney, 2 M. Regan, 1 M. Nakabayashi, 3 M. Buyse, 4 N. Clarke, 5 C. Tchou, 6 J. Dignam, 6 K. Fizazi, 7 M. Habibian, 8 S. Halabi, 9 P. Kantoff, 10 S. Williams 11

**Background:** The concept of surrogate endpoints emerged from the Food and Drug Administration’s (FDA) acceptance in 1992 of the time to metastasis (TTM) as a surrogate for survival in patients with metastatic castration-resistant prostate cancer (mCRPC).

**Methods:** By June 2013, we systematically identified 102 eligible randomized trials (n = 27,255) comparing CaP therapies. MFS was defined from randomization to death from any cause. We evaluated the surrogacy of MFS with OS from any cause; or was censored at the date of last follow-up. OS was defined from the first evidence of distant metastatic disease (excluding pelvic lymph nodes), or death due to any cause.

**Results:** By June 2013, we systematically identified 102 eligible randomized trials comparing CaP therapies. MFS was defined from randomization to death from any cause. We evaluated the surrogacy of MFS with OS from any cause; or was censored at the date of last follow-up. OS was defined from the first evidence of distant metastatic disease (excluding pelvic lymph nodes), or death due to any cause.

**Conclusion:** MFS is a surrogate for overall survival. The Intermediate Clinical Endpoints in CaP (ICECaP) Working Group is conducting meta-analyses of putative surrogate endpoints for localized CaP trials. We hypothesized that MFS is a surrogate for OS.

### Table: 717O

<table>
<thead>
<tr>
<th>Condition</th>
<th>Correlation between the ICE and true endpoint</th>
<th>r² from weighted linear regression of t-year Kaplan–Meier estimates (95% CI)</th>
<th>from weighted linear regression of treatment effects (log HR) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFS as surrogate for OS</td>
<td>5773%, 65</td>
<td>0.51 (0.42, 0.60)</td>
<td>0.42 (0.31, 0.53)</td>
</tr>
<tr>
<td>TTM as surrogate for DSS</td>
<td>2154%, 76</td>
<td>0.49 (0.40, 0.59)</td>
<td>0.41 (0.34, 0.50)</td>
</tr>
</tbody>
</table>

### Table: 718O

<table>
<thead>
<tr>
<th>Condition</th>
<th>Correlation between study-specific treatment effect on endpoints</th>
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<td>2154%, 76</td>
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</tbody>
</table>

### Conclusions:

MFS can be used as a surrogate of OS and TTM as a surrogate of DSS. The Intermediate Clinical Endpoints in CaP (ICECaP) Working Group is conducting meta-analyses of putative surrogate endpoints for localized CaP trials. We hypothesized that MFS is a surrogate for OS.

## PTEN loss as a predictive biomarker for the Akt inhibitor ipatasertib combined with abiraterone acetate in patients with metastatic castration-resistant prostate cancer (mCRPC)


**Background:** PTEN loss as a predictive biomarker for the Akt inhibitor ipatasertib combined with abiraterone acetate in patients with metastatic castration-resistant prostate cancer (mCRPC).

**Methods:** Pts with mCRPC, previously treated with docetaxel, were randomized 1:1:1 (double blinded) to 3 arms: Ipat-400 mg, Ipat-200 mg or placebo (Pbo) in combination to abiraterone acetate. These findings warrant the co-development of Ipat with a companion diagnostic assay to select mCRPC pts with PTEN loss and improve outcomes. NCT01485861.

**Conclusion:** This study indicates that combining Akt inhibition with improved AR pathway blockade in mCRPC may provide pt benefit and is the first clinical demonstration supporting PTEN loss as a predictive response biomarker for mCRPC.
D. Madayr: Employee and shareholder of Genentech/Roche. All other authors have declared no conflicts of interest.

First evidence of significant clinical activity of PD-1 inhibitors in metastatic, castration resistant prostate cancer (mCRPC)

J.N. Graff1, J.-L. Alunäck1, C.G. Drake2, G.V. Thomas3, W.L. Redmond4, M. Farhat5, R. Slottke6, T.M. Beer1

1Knight Cancer Institute, Oregon Health Science University, Portland, OR, USA, 2Sidney Kimmel Comprehensive Cancer Center and the Brady Urological Institute, Johns Hopkins University, Baltimore, MD, USA, 3Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Medical Center, Portland, OR, USA

Background: PD-1 inhibitor has demonstrated improved survival for patients with various solid tumors, but its role in prostate cancer has yet to be defined. Based on observations that PD-L1 expression is increased upon resistance to enzalutamide and androgen inhibition modulates the immune response to prostate cancer, we hypothesized that the addition of the PD-1 inhibitor pembrolizumab to enzalutamide at resistance could result in clinically important anti-tumor activity.

Methods: We treated men with mCRPC progressing on the androgen receptor antagonist enzalutamide on a phase II study of pembrolizumab 200 mg IV every 3 weeks for 4 doses with continued enzalutamide. Prior chemotherapy for mCRPC was prohibited. The primary endpoint is the proportion of men with a prostate specific antigen (PSA) response ≥ 50%. The secondary endpoints are objective disease response, PSA progression free survival, and overall survival. The sample size sufficient to detect a 25% response rate served as the basis for the statistical design. Tissue biopsy was performed if feasible.

Results: As of 22 Jul 2016, 20 patients have completed pembrolizumab treatment with a median follow up of 18 weeks. 4 of 20 subjects treated to date (20%) have achieved a PSA response ≥ 50%, reached a serum PSA ≤ 0.1 ng/ml and remain progression free after 16-61 weeks. 7 have stable disease of 9-50 weeks. 8 patients had progressive disease. 2 of the 4 PSA responders had measurable disease (liver, lymph nodes) and are evaluable for objective response. Both achieved a partial response and remain in response status after 61 and 22 weeks of follow up. Two of the responders were able to discontinue opioid analgesic after reporting resolution of cancer-related pain. 5 patients had significant immune-related adverse events (grade 2 myositis, grade 2 hypothyroidism, grade 2 hyperthyroidism, 2 grade 3 colitis) Immunochemistry from baseline biopsies of two responders showed the presence of CD3+, CD8+, and CD163+ leukocyte infiltrates and PD-L1 expression. 2 of the 4 responders had a tumor biopsy and 1 had micrometastatic instability in the tumor.

Conclusions: Early results demonstrate reproducible, profound, and - to date - durable responses to PD-1 inhibitor with enzalutamide in men with mCRPC.

Clinical trial identification: NCT02312557

Legal entity responsible for the study: Oregon Health & Science University

Funding: Merck Sharp & Dohme Corporation

Disclosure: J.N. Graff: I have received research funding from Merck to perform this research. I have received honoraria from Astellas C.G. Drake: Received research funding from Bristol Myers Squibb (BMS). He has received consulting fees from BMS, Merck, Astra Zeneca (AZ) and Medimmune. He has patents licensed from AZ and Medimmune. W.L. Redmond: Received research grant, consultancies, and/or royalties from Bristol-Myers Squibb, Merck, Galectin Therapeutics, and Nektar Therapeutics. T.M. Beer: Research funding from Astellas and Medivation; consulting fees from Astellas. All other authors have declared no conflicts of interest.

Long term efficacy and QOL data of chemohormonal therapy (C-HT) in low and high volume hormone naive metastatic prostate cancer (mCastr) E3805 CHAARTED trial


1Lank Center for Genitourinary Oncology, Dana Farber Cancer Institute, Boston, MA, USA, 2Biostatistics, Dana-Farber Cancer Institute, Boston, MA, USA, 3Oncology, UW Carbone Cancer Center, Madison, WI, USA, 4Oncology, Johns Hopkins Hospital, Baltimore, MD, USA, 5Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, 6Medical Oncology, The University of Chicago Medical Centre, Chicago, IL, USA, 7Medical Oncology, Mayo Clinic, Rochester, NY, USA, 8Medical Oncology, University Hospitals Case Medical Center, Cleveland, OH, USA, 9Medical Oncology, University of Virginia, Charlottesville, VA, USA, 10Medical Oncology, US Oncology Research c/o Comprehensive Cancer Ctr of NV, Las Vegas, NV, USA, 11Medical Oncology, Washington University School of Medicine, St Louis, MO, USA, 12Medical Oncology, NorthShore University HealthSystem, Chicago, IL, USA, 13Medical Oncology, University of Michigan, Ann Arbor, MI, USA, 14Medical Oncology, Cleveland Clinic Foundation, Cleveland, OH, USA, 15Medical Oncology, University of Kentucky, Lexington, KY, USA

Background: Early analyses revealed significant increase in overall survival (OS) for patients with a higher burden of disease with early docetaxel (D) plus androgen deprivation therapy (ADT) over ADT alone. Patients with low volume disease have a more favorable natural history with ADT alone and the benefit of early D for this distinct subset requires longer follow-up.

Methods: 790 men were accrued from 7/28/06 to 11/21/2012 and randomized to ADT alone or ADT + D at 75mg/m2 every 3 weeks for 6 cycles within 4 mos of ADT. Patients were prospectively stratified into high volume (HV) vs. low volume (LV) disease (HV: visceral metastases and/or 4 or more bone metastases with at least one outside of the vertebral column and pelvis).

Results: As of April 23, 2016, the median follow-up was 53.7 months and there were 299 deaths of 513 HV pts and 100 deaths of the 277 LV pts. The overall median OS was 57.6 mos for ADT + D [95% CI: (52.0, 63.9)] and 47.2 (41.8, 52.8) for ADT alone. HR = 0.73 (0.59, 0.89), p = 0.0018 (stratified log rank). Deaths and distribution of OS by arm and volume of disease are in Table 1. The evaluation of outcome by disease volume interaction with treatments revealed a p-value 0.029 indicating the impact of early docetaxel differed between the HV and LV pts. The burden of cancer and therapy was assessed by FACT-P score and notable findings were (i) LV pts had lower baseline FACT-P score than HV, (ii) there was a decline in QOL from baseline to 3 months in ADT + LV pts and (iii) the lowest FACT-P score at 12 months was in ADT alone HV pts (see Table).

Table: 720PD

<table>
<thead>
<tr>
<th>Survival</th>
<th>ADT + D</th>
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<tbody>
<tr>
<td>LV Deaths / N (%)</td>
<td>51/134 (38.1%)</td>
<td>48/143 (34.3%)</td>
</tr>
<tr>
<td>LV Median OS mos*</td>
<td>63.8 (58.8, 78.5)</td>
<td>107/269 (52.1%)</td>
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<td>HV Deaths / N (%)</td>
<td>127/269 (48.4%)</td>
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</tr>
<tr>
<td>HV Median OS mos*</td>
<td>51.2 (45.2, 58.1)</td>
<td></td>
</tr>
<tr>
<td>Mean FACT-P scores (SE)</td>
<td>34.4 (31.0, 42.1)</td>
<td></td>
</tr>
<tr>
<td>LV Baseline</td>
<td>N = 234</td>
<td></td>
</tr>
<tr>
<td>LV 3 months</td>
<td>N = 223</td>
<td></td>
</tr>
<tr>
<td>LV 12 months</td>
<td>N = 170</td>
<td></td>
</tr>
<tr>
<td>LV Baseline</td>
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<tr>
<td>LV 3 months</td>
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<td></td>
</tr>
<tr>
<td>LV 12 months</td>
<td>N = 109</td>
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</tr>
</tbody>
</table>

*Stratified on baseline factors Cox proportional hazards model for evaluation of treatment effect on overall survival. CI: confidence intervals; N: number of patients; HR: Hazard ratio; SE: standard error

Conclusions: The clinical benefit of ADT + D is limited to pts with a higher burden of metastatic prostate. Partial Support and drug supply by Sanofi.

Clinical trial identification: NCT00309985

Legal entity responsible for the study: NCI

Funding: NCI

Disclosure: C. Sweeney: Grant support from the NCI, personal fees from Sanofi, Janssen, Astellas, Bayer, and Genentech. G. Liu: Dr. Liu reports grant support from the University of Wisconsin Carbone Cancer Center during the conduct of the study. M. Carducci: Dr. Carducci reports personal fees from Sanofi, Amgen, Astellas, and Medivation outside the submitted work. M. Eisenberger: Dr. Eisenberger reports other fees from Sanofi outside the submitted work. Y. N. Wong: Dr. Wong reports other fees from Sanofi outside the submitted work. R. Dresier: Dr. Dresier reports personal fees from Millennium, Medivation, Astellas, Bind Pharmaceuticals, Genentech, Roche, and Daiichi Sankyo outside the submitted work.

Table 720PD: Survival data for the CHAARTED trial

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*Stratified on baseline factors Cox proportional hazards model for evaluation of treatment effect on overall survival. CI: confidence intervals; N: number of patients; HR: Hazard ratio; SE: standard error


**Prostate Cancer**

**FIRSTANA: Health-related quality of life (HRQL) and post-hoc analyses for the phase III study assessing cabazitaxel (C) vs docetaxel (D) in chemotherapy-naive patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)**


**Background:** FIRSTANA (NCT01308567), a post-marketing assessment, reported the superiority of C20 and C25 mg/m2 (C20, C25) vs D in terms of overall survival (OS), in chemotherapy-naive mCRPC pts. **Methods:** Pts were randomized 1:1:1 to receive C20, C25 or D (plus prednisone). Primary endpoint was OS. Secondary endpoints: safety, progression-free survival (PFS), prostate-specific antigen (PSA) and tumor response (TR), HRQoL (Functional Assessment of Cancer Therapy-Prostate [FACT-P] questionnaire) and pain response (PR). **Results:** OS, PFS and PSA response were not significantly different; TR was superior for C25 vs D (Table). Rates of Grade 3–4 treatment-emergent adverse events were C20 42.1%, C25 60.1%; D 46.0%. Change from baseline to Cycle 16 in FACT-P total score differed between the C20 and D arms. Grade 3 neutropenia and NLR < 3 were associated with increased OS in all arms.

![Table: Table 721PD](image)

**Conclusions:** In chemotherapy-naive mCRPC pts, OS was not superior for C20 vs C25. OS was significantly higher for C25 vs D. C20 may have greater HRQoL benefit than D. Grade 3–4 neutropenia and low NLR correlated with increased OS and may have prognostic value. Funding: Sanofi Genzyme.

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**Proselica: Health-related quality of life (HRQL) and post-hoc analyses for the phase 3 study assessing cabazitaxel 20 (C20) vs 25 (C25) mg/m2 post-docetaxel (D) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)**


**Background:** PROSELICA (NCT01308580) was a post-marketing request to demonstrate non-inferiority of C20 vs C25 in terms of overall survival (OS) in mCRPC pts who progressed on D. **Methods:** Post-D mCRPC pts were randomized 1:1 to receive C25 or C20 (+ prednisone). To show non-inferiority of C20 (preservation of C25 efficacy over mitoxantrone in the TROPIC trial) with 95% confidence interval (CI), hazard ratio (HR) could not exceed 1.214 under a 1-sided 98.89% CI after interim analyses. Secondary endpoints: progression-free survival (PFS), prostate-specific antigen (PSA) and tumor response (TR), safety, HRQoL (Functional Assessment of Cancer Therapy-Prostate [FACT-P] questionnaire) and pain response (PR). **Results:** Pts were randomized (580 vs 552). BL pts characteristics were similar for C20 and C25. See Table for efficacy results. Rates of Grade 3–4 treatment-emergent adverse events were 39.7% C20, 54.5% C25. Change in FACT-P total score from BL was not significantly different for C20 and C25. Grade 3–4 neutropenia on treatment and BL NLR < 3 was associated with increased OS in both arms (Table).

![Table: Table 722PD](image)

**Conclusions:** In post-D mCRPC pts, OS was not significantly different for C20 vs C25 in terms of overall survival (OS) in mCRPC pts who progressed on D.
Background: The patterns of relapse in patients with high-risk prostate cancer treated with modern therapy are poorly described. In the present study, we aimed to analyse the patterns of relapse in the randomized phase III trial Groupe d’Etude des Tumeurs Uro-Genitales 12 (GETUG 12) in patients with high-risk localised prostate cancer.

Methods: Patients were enrolled and randomly assigned to receive either androgen deprivation therapy (ADT) with goserelin every 3 months for 3 years combined upfront with 4 cycles of docetaxel and estramustine (ADT + DE) or ADT alone, plus local therapy as per investigator’s analysis. Least square-free-survival (LSFS) analysis were performed with biochemical progression (bPS). Adjusting factors were stratification factors (T stage, Gleason score, baseline PSA, and n status) and treatment.

Results: 413 patients were randomized from 2002 to 2006, 206 treated with ADT alone and 207 with ADT + DE. Median follow-up was 8.8 years (IQR: 8.1-9.7). A total of 130 patients exhibited biochemical relapse, with a median bPS of 5 years (range: 0.23-10.4) for relapsing patients. 77/130 patients subsequently developed a second event: metastatic progression (33%), clinical progression (13%) and death (7%). The analysis of relapsing patients revealed the following data: 1) the median time from biochemical failure to a clinical event was 2 years (95% CI: 1.0 - 2.91), 2) biochemical relapses were rare (n = 27; 21%) within the first year (3-3 years) with most relapses (n = 105; 79%) occurring after 3 years (≥3 years), 3) the timing of the relapse (<3 years) exerted a major prognostic impact: 26/27 patients (96%) relapsing within 3 years and 31/103 patients (30%) relapsing ≥3 years developed a second event (adjusted hazard ratio: 0.53 (95% CI 0.32-0.88), p = 0.014).

Conclusions: This analysis of the GETUG 12 trial demonstrates that overall, a clinical event is to be expected, with a median time of 2 years in patients with high-risk localised prostate cancer who develop a biochemical relapse, and that the timing of this relapse is highly prognostic with twice as many clinical events likely to occur in patients relapsing within the first 3 years.

Clinical trial identification: GETUG 12: ClinicalTrials.gov NCT00053731

Legal entity responsible for the study: Institut Gustave Roussy

Funding: N/A

Disclosure: A. Fechon; Sanofi; S. Oudard; Sanofi, Bayer, Astellas, Janssen. K. Fizzi: Participation in advisory boards and honorarium. Sanofi. All other authors have declared no conflicts of interest.

Risk of prostate cancer mortality in men with an initial benign needle core biopsy set: a population based analysis with up to 20 years of follow-up

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Background: It has been questioned whether systematic transrectal ultrasound-guided biopsies (TRUS-bi) miss significant prostate cancers (PCa). MRI guided biopsies have been proposed for men where the initial TRUS-bi was normal and may increase sensitivity and detection of significant PCa, a definition based on the presence of a Gleason grade 4 or more in the biopsies. In 2010, Schröder et al. demonstrated with data from the ERSPC-study, that 0.03% of men with an initial, normal biopsy set died from PCa after 11 years of follow-up. Here, we calculate the risk of PCa-specific mortality in men with an initial, benign biopsy set, in the complete nation-wide cohort of men who underwent evaluation for PCa with TRUS-bi during a 16-year period, in which systematic PSA screening or MRI was not part of the first biopsy setup.

Methods: Data originate from the Danish Prostate Cancer Register (DaPCaR). All men undergoing their first TRUS-bi in 1995-2011 were identified. Risk of PCa-specific mortality was analyzed in a competing risk setting treating death from non-PCa as competing risk.

Results: 64,430 men were referred for TRUS-bi. A total of 27,537 men had a benign first biopsy set, and 8,526 of these underwent a re-biopsy procedure. Median follow-up was 7.1 years. After 20 years, the estimated cumulative incidence of PCa mortality and other-mortality was 5.2% and 59.9% respectively. For men with an initial, benign TRUS-bi, the cumulative incidence of PCa mortality and other-mortality was 5.2% and 59.9% after 20 years. When stratified for level of PSA at time of referral, the estimated risk of PCa mortality after 15 years in men with a benign, first TRUS-bi was 0.7% for PSA ≤10 µg/L, 3.6% for PSA >10 - ≤20 µg/L, and 17.6% for PSA > 20 µg/L.

Conclusions: Our data demonstrate, that the first systematic TRUS-bi does indeed diagnose patients at risk of PCa death. Our study supports the results from ERSPC, underlining that men with low PSA and an initial normal TRUS-bi rarely harbor lethal PCa. This information has implications for the future strategy of how to advise men with benign biopsies.

Legal entity responsible for the study: N/A

Funding: The Danish Cancer Society, The Capital Region of Danmarks Fund for Health Research, Krista and Viggo Petersens Foundation

Disclosure: All authors have declared no conflicts of interest.
Early responses to enzalutamide in AR-V7 positive first line metastatic castration-resistant prostate cancer (mCRPC): a prospective SOGUG clinical trial: THE PREMIERE study

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Background: AR-V7 has been proposed as a biomarker for early resistance to enzalutamide in heavily pretreated mCRPC patients (pts). Methods: Phase II open-label study in chemo-naïve mCRPC patients. Results: 98 pts were included between February 5th and November 23th 2015. Pts characteristics are: median age 77.8y; ECOG 0/1 in 55/45%, median basal PSA 20 ng/dl (range 5.5-20 000 ng/dl). Radiologic response was: PR 12.5%, SD 77.1% and PD 10.4%. Basal CTCs were processed utilizing the Epic Sciences CTC nuclear AR-V7 protein test. Patients were stratified according to AR-V7 status and treatment assignment. Positive AR-V7 CTC nuclear protein was lower than that of AR-V7 mRNA, but more predictive of ARSi outcomes. Conclusion: AR-V7 is a truncated form of the AR lacking the ligand binding domain that activates AR signaling in the absence of androgens. The presence of AR-V7 mRNA in CTCs predicts a poor outcome on the ARSi, abiraterone acetate (AA) and enzalutamide. Localization of AR-V7 in the nucleus of CTCs also predicts poor ARSi outcomes, and a treatment-specific interaction that predicted a reduced risk of death if Taxanes vs. ARSi (HR = 0.242, p < 0.0350) was prescribed. Overall, the incidence of nuclear AR-V7 protein was lower than that of AR-V7 mRNA, but more predictive of ARSi outcomes. In a post-hoc analysis of outcomes of samples evaluated with AR-V7 CTC protein we asked if the presence of cytoplasmic AR-V7 protein could explain the difference in prognostic ability of the two tests, and separately, explored the association between non-nuclear AR-V7 and benefit from taxanes over ARSi.

Impact of AR-V7 protein localization in the prediction of therapeutic benefit of taxanes over androgen receptor signaling inhibitors (ARSi) in metastatic castration resistant prostate cancer (mCRPC)

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1Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, 2Translational Research, Epc Sciences, Inc, San Diego, CA, USA, 3Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background: AR-V7 is a truncated form of the AR lacking the ligand binding domain that activates AR signaling in the absence of androgens. The presence of AR-V7 mRNA in CTCs predicts a poor outcome on the ARSi, abiraterone acetate (AA), and enzalutamide. Localization of AR-V7 in the nucleus of CTCs also predicts poor ARSi outcomes, and a treatment-specific interaction that predicted a reduced risk of death if Taxanes vs. ARSi (HR = 0.242, p < 0.0350) was prescribed. Overall, the incidence of nuclear AR-V7 protein was lower than that of AR-V7 mRNA, but more predictive of ARSi outcomes. In a post-hoc analysis of outcomes of samples evaluated with AR-V7 CTC protein we asked if the presence of cytoplasmic AR-V7 protein could explain the difference in prognostic ability of the two tests, and separately, explored the association between non-nuclear AR-V7 and benefit from taxanes over ARSi.

Methods: 191 blood samples (n = 128 pre-ARSi, n = 63 pre-Taxane) from 161 patients were processed utilizing the EpiSciences CTC nuclear AR-V7 protein test. Patients...
were followed up to 29.5 months (range 1.3 to 29.5). Samples were rescued by readers, blinded to outcome, to determine the frequency of and outcome with cytoplasmic AR-V7.

Results: Inclusion of non-nuclear localized AR-V7 protein as positive scoring criteria increased the incidence of detection in all lines of therapy, an equivalent increase in false positives (PSA responders), and loss of the significance of the treatment-specific survival interaction in multivariate model.

Conclusions: Including cytoplasmic AR-V7 in the “positive” test definition reduces the prognostic power of the assay and negates the treatment predictive value of AR-V7. Not all AR-V7 signal is equivalent. It remains to be seen if non-nuclear localized AR-V7 protein samples would test positive via mRNA method.

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center

Funding: Epic Sciences

Disclosure: H. Scher: Consulting: Astellas, AstraZeneca, BIND Therapeutics, Blue Earth, Bristol-Myers Squibb, Chugai, Endocyte, Ferring, Genentech, Janssen, Med IQ, Medivation, OncologySTAT, Palmetto GBA, Pfizer, Sanofi, Takeda, Ventana, WIRB-Copernicus Group. R. Graf, D. Lu, J. Louw, R. Dittamore: Epic Sciences Employee. All other authors have declared no conflicts of interest.

**Table 728PD**

<table>
<thead>
<tr>
<th>AR-V7 Localization</th>
<th>Detection Rate by Line of Therapy (1,2)</th>
<th>HR of OS on Therapy Interaction (Taxanes vs. ARs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear (alone)</td>
<td>3%, 18%, 31%</td>
<td>11.5, p &lt; 0.0001 0.242, p &lt; 0.050</td>
</tr>
<tr>
<td>Cytoplasmic (alone)</td>
<td>18%, 8%, 12%</td>
<td>1.11, p = 0.844 1.21, p = 0.858</td>
</tr>
<tr>
<td>Any (Nuc &amp; Cyto)</td>
<td>16%, 26%, 43%</td>
<td>4.93, p &lt; 0.0001 1.04, p = 0.943</td>
</tr>
</tbody>
</table>

Background: The androgen receptor splice variant 7 (AR-V7) is associated with resistance to hormonal therapy in castration resistant prostate cancer (CRPC). Due to the limitations of methods available for AR-V7 analysis, the identification of a reliable detection method may facilitate the use of this biomarker in clinical practice. In order to provide a reliable laboratory approach to AR-V7 assessment, the present study was conducted to: 1) confirm the role of AR-V7 in prediction of resistance to hormonal therapy; 2) develop a new methodological approach to reliably and easily assess AR-V7 detection method may facilitate the use of this biomarker in clinical practice. In order to provide a reliable laboratory approach to AR-V7 assessment, the present study was conducted to: 1) confirm the role of AR-V7 in prediction of resistance to hormonal therapy; 2) develop a new methodological approach to reliably and easily assess AR-V7.

Results: 99% of patients were found carriers of the AR-V7 transcript. Twenty-six patients received abiraterone and 10 enzalutamide. The median clinical or radiographic progression free survival was significantly longer in AR-V7 negative compared to positive patients (20 vs 3 months, P < 0.001). Overall survival was significantly shorter in men with detectable AR-V7 at baseline compared to those with undetectable AR-V7 (median 8 months vs not reached (P < 0.001). In the AR-V7 positive patients, the PSA response rate was 7% (1 out of 14 men), while in the AR-V7 negative patients the PSA response rate was 64% (14 of 22 men). The AR-V7 positive subjects were more likely to be younger, Gleason Score at least 8. visceral metastasis, higher PSA levels, and prior docetaxel treatment than AR-V7 negative patients.

Conclusions: The present study demonstrates that plasma-derived exosomal RNA is a reliable source of AR-V7 and its detection predicts resistance to anti-hormonal therapy. The method is sensitive, fast and represents a convenient alternative to other potentially more expensive and less sensitive approaches, i.e., circulating tumor cells.

Legal entity responsible for the study: Prof. Romano Danesi

Funding: Academic funding

Disclosure: All authors have declared no conflicts of interest.

**Table: 728PD**

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<th>Therapy Interaction</th>
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**Phase 1 study of the PSMA-targeted tubulin small-molecule drug conjugate EC1169 in patients with metastatic castrate-resistant prostate cancer (mCRPC): Study update**

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Background: Prostate-specific membrane antigen (PSMA) is overexpressed by most prostate cancers. EC1169 is a conjugate of a PSMA-targeting moiety linked to the cytotoxic agent tubulysin B hydrazide (TubHB). Following internalization of IC1169 by targeted cancer cells, intracellular release of TubHB results in inhibition of tubulin
polymerization. In PSMA-positive LNCaP and MDA PCa 2b xenografts, complete responses and cures have been observed following EC1169 treatment. EC1169 does not show activity in PSMA-negative models, demonstrating its specificity. EC0652 is a companion radio-diagnostic conjugate of a 99mTc chelator and a PSMA-targeting moiety designed to characterize PSMA-expressing prostate cancer in real time: Rapid tumor uptake of 99mTc-EC0652 and rapid normal tissue clearance result in enhanced tumor-to-background ratios with SPECT imaging.

Methods: Key inclusion criteria are age ≥18 years, ECOG PS 0–1, and adequate organ function. Patients (pts) must have failed androgen-deprivation therapy, progressed on abiraterone or enzalutamide, and have been previously treated with a taxane unless contraindicated. Patients are to undergo a 3+3 EC0652 SPECT scan prior to therapy. PSMA positivty is not a requirement for study entry. EC1169 is administered as an intravenous bolus on Days (D) 1, 8, and QW every 21 D. Dose escalation is based upon the ‘3 + 3’ method. Study objectives include determination of EC1169 MTD and recommended phase II dose, safety, pharmacokinetics, antitumor activity and its correlation with PSMA expression as identified on 99mTc-EC0652 SPECT imaging.

Results: 23 pts have been treated on the QW schedule. Median age is 70 range: 57–82. The median number of administered EC1169 cycles is ≥2 (range: 1–12). 12 (52%) treatment related AEs have been reported. Most common Grade 3/4 AEs were anaemia (2, 8.7%) and lymphopenia (2, 8.7%). No DLT, related SAEs or toxicity requiring dose reductions occurred. PSA response (≥50% max decline) has been observed in 2 pts. Data will be presented.

Conclusions: To date, EC1169 has been well tolerated. There are promising signs of early efficacy in this heavily pretreated population.

Clinical trial identification: ClinicalTrials.gov NCT02202447

Legal entity responsible for the study: Endocyte, Inc.

Funding: Endocyte, Inc.

Disclosure: M.J. Morris: MSECC receives funding from Endocyte for the conduct of this study. I have received funding for advisory boards from Progenesis, Tokai, & Millennium Pharmaceuticals. I’m an uncompensated advisor for Bayer, which my institutions receives funding. O. Santor, S. Mott. Endocyte: consultancy fees. A. Armour: Alison Armour is an employee of Endocyte. H.M. Bahler: Endocyte: consultancy fees. Celgene: Consultant/Advisory Board. SirTex: Honorarium. All other authors have declared no conflicts of interest.

### A phase II study of TKI258 in patients with castration-resistant prostate cancer (KCSG-GU11-08)


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Background: FGFR signals are important in carcinogenesis and progression of prostate cancer. TKI258 (dovitinib) is an oral, pan-class VEGFR, PDGFR, and FGFR inhibitor. Preclinical data demonstrated a significant activity of TKI258 in mouse xenograft models. We evaluated the efficacy and toxicity of TKI258 in men with metastatic CRPC.

Methods: This study was a single-arm, phase II, open-label, multicenter trial of TKI258 (500mg orally according to a 5-days-on and 2-days-off schedule). The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), toxicity and PFS rate. Biomarker analysis for serum FGFR, FGF-23 and VEGFR using multiplex ELISA were performed. This study is registered with ClinicalTrials.gov, number NCT01741116.

Results: Forty-four men were accrued from 11 hospitals: 80% post-docetaxel; median PSA was 100 ng/dl, median age was 69, 82% had bone metastases, 25% had liver metastases. Median cycles of TKI258 was 2 (range 0-33). Median PFS was 6.67 months (95% CI: 3.56-8.79) and median OS was 13.7 months (95% CI 7.09-20.36). Chemotherapy-naive patients had longer PFS (17.9 months, 95% CI: 9.23-28.57) compared with docetaxel-treated patients (2.07 months, 95% CI: 1.73-2.41, p = 0.001) and the patients with high serum VEGFR2 level over median level (7800 pg/ml) showed longer PFS compared with others (6.03 months, 95% CI: 4.26-7.80) vs 1.97 months (95% CI: 1.79-2.15 months, p = 0.023). The PSA decline was observed in 32.3% and 12.9% of patients achieved ≥ 50% decline. Four objective responses were observed with ORR of 12.5% (95% CI: 0.28-0.16). Grade 3 related AEs were seen in 40.9% of patients with 7.0% stopping TKI258 due to toxicity. The most common related AEs included grade 1-2 nausea, diarrhoea, fatigue, anorexia and all grade thrombocytopenia (29.5%).

Conclusions: TKI258 showed modest antitumor activity with manageable toxicities in men with mCRPC. Especially, patients who were chemo-naive or with high levels of serum VEGFR2 had the benefit from TKI258.

Clinical trial identification: ClinicalTrials.gov NCT01741116

Legal entity responsible for the study: KCSG (Korean Cancer Study Group)

Funding: KCSG (Korean Cancer Study Group)

Disclosure: All authors have declared no conflicts of interest.
Methods: Men aged ≥18 y with intermediate risk localised PC appropriate for EBRT were deemed at high risk. Metastatic PCa was defined by baseline TNM staging (M1). High risk PCa was defined as baseline PSA >20 ng/ml or Gleason score >8–10. Pts in the American (n = 60), European (n = 24), and Middle Eastern (n = 224) were randomized to receive degarelix (n = 193), or LH-RH agonist (n = 188). PSA-PFS was defined as death from any cause or PSA recurrence (two consecutive increases ≥50% [≥2 weeks apart] and ≥0.2 ng/ml increase from nadir). Unadjusted Kaplan-Meier analyses (log-rank test) and Cox-proportional hazard models (Wald Chi-square p-value) were used (stratified by baseline PSA categories, and adjusted for treatment, PCa stage, age and region) to assess treatment differences in PSA-PFS.

Results: PSA-PFS was significantly improved in the degarelix group among metastatic or high risk pts (p = 0.011). Region did not influence difference between antagonist and agonist in PSA-PFS (treatment-by-region interaction p = 0.884). However, Chinese (HR = 0.48 [95% CI: 0.31–0.74]) and American (HR = 0.28 [95% CI: 0.10–0.76]) pts had lower risk for PSA-PFS compared to European pts. There was a lower hazard for PSA-PFS with degarelix across all regions when stratifying for PSA (and adjusting for confounders); HR = 0.67 (95% CI: 0.44–0.91) p = 0.035.

Conclusions: Improved PSA-PFS was shown in pts treated with degarelix vs LH-RH agonists in metastatic or high risk PCa pts irrespective of region. These results suggest delayed disease progression with initial use of a GnRH antagonist as compared with LH-RH agonists across global regions.

Legal entity responsible for the study: Ferring Pharmaceuticals

Funding: Ferring Pharmaceuticals


**Table: 734P**

<table>
<thead>
<tr>
<th>Table: 734P</th>
<th>Median (range)</th>
<th>After 24 Wks</th>
<th>4 Wks Post-Rx Discontinuation</th>
<th>8 Wks Post-Rx Discontinuation</th>
<th>12 Wks Post-Rx Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RGX LH, IU/L</td>
<td>4.7 (0.8–32.2)</td>
<td>0.1 (0.1–3.9)</td>
<td>3.1 (0.2–15.7)</td>
<td>8.3 (0.1–32.4)</td>
<td>10.7 (0.1–38.7)</td>
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<td>DGC LH, IU/L</td>
<td>4.8 (1.3–42.0)</td>
<td>0.1 (0.1–3.7)</td>
<td>0.2 (0.1–2.8)</td>
<td>0.5 (0.1–7.7)</td>
<td>1.4 (0.1–15.7)</td>
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<td>RGX T, ng/dL</td>
<td>355.9 (149.0–1290.0)</td>
<td>8.1 (3.2–123.5)</td>
<td>9.4 (2.9–818.8)</td>
<td>238.4 (1.0–929.8)</td>
<td>257.0 (9.5–858.8)</td>
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<td>DGX T, ng/dL</td>
<td>404.0 (138.0–727.8)</td>
<td>9.9 (2.9–272.8)</td>
<td>9.7 (2.9–223.0)</td>
<td>16.1 (3.2–203.0)</td>
<td>20.0 (3.7–378.8)</td>
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<td>RGX PSA, ug/L</td>
<td>7.3 (2.6–31.5)</td>
<td>0.1 (0.1–1.6)</td>
<td>0.1 (0.1–1.5)</td>
<td>0.19 (0.1–3.2)</td>
<td>0.19 (0.1–2.3)</td>
</tr>
<tr>
<td>DGX PSA, ug/L</td>
<td>7.3 (2.3–88.9)</td>
<td>0.1 (0.1–1.8)</td>
<td>0.1 (0.1–2.1)</td>
<td>0.1 (0.1–2.2)</td>
<td>0.07 (0.1–2.0)</td>
</tr>
</tbody>
</table>
Annals of Oncology

pantoprazole can prevent or delay resistance to docetaxel via the inhibition of autophagy in several solid tumour xenografts.

Methods: Men with chemotherapy-naïve mCRPC with a PSA >10ng/ml and adequate organ function were eligible for enrolment. The study regimen included intravenous pantoprazole (240mg) and docetaxel (75mg/m²) every 21 days, with continuous prednisone 5mg twice daily. The primary endpoint was a confirmed ≥50% decline of PSA. Progression free (PFS) and overall survival (OS) were assessed by the Kaplan-Meier method. This trial used a Simon’s 2-stage design. The estimated median PFS was 5.3 months (95%CI: 2.6-12.9) and median OS was 15.7 months (95% CI: 9.3-19.6). There were no toxic deaths and most adverse events were attributed to docetaxel (hematological: 14% febrile neutropenia, 14% G4 neutropenia, 19% G3/4 anemia; non-hematological: 24% G3 fatigue and 5% G3 anorexia).

Results: Between November 2012 and March 2015, 21 men with a median age of 70 years (range 58-81 years) were treated (median 6 cycles, range 2 to 11). Participants (pts) had received prior systemic therapies (median 4, range 1 to 8) and 14 had received abiraterone, and/or enzalutamide. The PSA response rate was 52% (11/21) which did not meet the prespecified criterion (≥12/21 responders) to proceed to stage 2 of the study. At interim analysis with a median follow-up of 12 months, 13 (62%) pts were deceased (10 CRPC, 2 unknown, 1 radiation complication). Of the pts with RECIST measurable disease, the radiographic partial response rate was 31% (4/13). The combination of docetaxel and pantoprazole was tolerable, but the resultant clinical activity was not sufficient to meet the ambitious predefined target to warrant further testing. Planned correlative studies to evaluate tumor samples for the possibility of identifying this molecularly distinct group using non-invasive imaging methods.

Conclusions: The combination of docetaxel and pantoprazole was tolerable, but the resultant clinical activity was not sufficient to meet the ambitious predefined target to warrant further testing. Planned correlative studies to evaluate tumor samples for the possibility of identifying this molecularly distinct group using non-invasive imaging methods.

Clinical trial identification: NCT01748500

Legal entity responsible for the study: Princess Margaret Cancer Centre

Funding: Supported by a grant from the Canadian Institutes of Health Research.

Disclosure: All authors have declared no conflicts of interest.

Increased choline uptake in androgen receptor (AR) copy number gain castration-resistant prostate cancers (CRPC)

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Background: Preliminary data suggests an association between choline uptake and androgen receptor (AR) expression with upregulation of choline kinase alpha protein in prostate cancer. We aimed to make a direct comparison between AR copy number variations (CNV) and 18F-fluorocholine (FCH) uptake on PET/CT in patients with metastatic CRPC.

Methods: We determined AR CNV by digital droplet PCR and Taqman on pre-treatment plasma from 80 patients with metastatic CRPC, progressing after docetaxel treated with abiraterone (n = 47) or enzalutamide (n = 33) as described previously (Romani et al. Sci Transl Med 2015; Salvi et al, Br J Cancer 2015; Salvi et al, Oncotarget 2016). For all patients, an FCH PET/CT scan was performed at baseline and total lesion activity (TLA) and metabolic tumor volume (MTV) calculated. The primary end point was the correlation between circulating AR CNV and TLA and MTV. The secondary end points were progression-free survival (PFS) and overall survival (OS) stratified by circulating AR CNV and TLA/MTV.

Results: We observed AR copy number gain in 24 (30%) of 80 patients, 14 (30%) of 47 patients treated with abiraterone and 10 (29%) of 33 treated with enzalutamide. The number of metastatic lesions and previous therapeutic lines were higher in the enzalutamide group (P = 0.03 and P = 0.02, respectively). We observed a significant correlation between AR gain and TLA and MTV values (P = 0.001 and P = 0.004, respectively, R0.36). Multivariate analysis revealed that AR CNV and TLA value were associated with both shorter PFS (P < 0.0009 and P = 0.028, respectively) and OS (P = 0.031 and P = 0.039, respectively).

Conclusions: Choline uptake is higher in AR gain cancers. This introduces the possibility of identifying this moleculely distinct group using non-invasive imaging and supports the hypothesis of increased choline uptake in cancers overexpressing AR.

Legal entity responsible for the study: Ugo De Giorgi

Funding: IRST BRCs

Disclosure: All authors have declared no conflicts of interest.

Meta-analysis of randomized clinical trials in metastatic castration resistant prostate cancer: Comparison of enzalutamide and abiraterone acetate plus prednisone treatment

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Background: Enzalutamide (ENZ) and abiraterone acetate (AA) are oral hormonal agents for the treatment of metastatic castration resistant prostate cancer (mCRPC) patients. Although these two drugs target the androgen signaling pathway, they have different mechanisms of action, with ENZ targeting the androgen receptors1 whilst abiraterone targeting the activity of CYP172. Consequently, they also differ in the nature of their adverse events profile

Methods: Following a meta-analysis presented at ASCO GU 20162 on fatigue and cardiovascular adverse events (AEs) a further analysis, using the same methodology, was performed on hypertension, neurological and psychiatric AEs based on a literature search of randomized controlled trials (RCTs) that included AA + prednisone (P) or ENZ. The risk of these AEs was assessed by the overall relative risk of all the RCTs that comply with the inclusion criteria. Summary of incidence, relative-risks (RR), and 95% confidence intervals (CI) were calculated using random-effects or fixed-effects models based on the heterogeneity of included studies.

Results: RR for hypertension (all grades) was 2.26 (1.06-4.81) for ENZ and 1.61 (1.30-2.00) for AA + P, for hypertension grade ≥2 was 2.52 (1.63-3.95) and 1.72 (0.97-3.08) respectively. The RR for neurological disorders was 1.44 (1.31-1.58) for ENZ and 1.13 (0.99-1.29) for AA + P RR for psychiatric disorders was 1.43 (1.21-1.69) for ENZ and 1.04 (0.9-1.20) for AA + P. No evidence of publication bias was observed.

Conclusions: The aim of this study is to contrast the hypertension, psychiatric and central nervous system disorders safety profile of AA + P and ENZ. This analysis suggests that mCRPC patients treated with ENZ had a higher risk of developing hypertension, neurological and psychiatric disorders than the patients treated with AA + P. One may speculate that the affinity of ENZ for GABA receptor may play a role in the toxicities related to the central nervous system.

Legal entity responsible for the study: Janssen. Funding: janssen, Spain


Fatigue in men with metastatic castration-resistant prostate cancer treated with enzalutamide: data from randomised clinical trials


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Background: Fatigue is common in men with advanced prostate cancer and may be related to disease progression, ongoing systemic therapy, comorbidities, concomitant medications or a combination of these factors. Fatigue adverse events (AEs) across four double-blind, randomised, placebo- or bicalutamide-controlled trials of enzalutamide (ENZA) for men with metastatic castration-resistant prostate cancer are summarised to assess incidence, timing and effect of age on fatigue

Methods: Safety data from ENZA trials (AFFIRM NCT00974311, PREVAIL NCT0112991, TERRAIN NCT01288911 and STRIVE NCT01664923) with men with metastatic castration-resistant prostate cancer were evaluated for fatigue AEs. As per CTCAE, v 4.0, fatigue is defined as a state of generalized weakness, with a pronounced inability to summon sufficient energy to accomplish daily activities. Analyses included unadjusted and per-100 patient-years fatigue AE incidences assessed by grade, time and age (<75 or ≥75 years).

Funding: data from ENZA trials (AFFIRM NCT00974311, PREVAIL NCT0112991, TERRAIN NCT01288911 and STRIVE NCT01664923) with men with metastatic castration-resistant prostate cancer were evaluated for fatigue AEs.
Results: With 2051 men in the ENZA arms and 1630 in the control arms, total treatment exposure patient-years were longer for ENZA (range, 219-1249 vs control range, 143-560). The unadjusted percentages of men reporting fatigue for all grades were slightly higher in the ENZA arms (range, 28% vs 28% vs the control arms (range, 29% vs 29%). Grade 3 fatigue was reported by 10% of men and in similar proportions in both arms (1% for ENZA vs 1% vs 7% for control). The exposure-adjusted incidence rates of fatigue AEs were similar or lower in the ENZA arms vs the control arms (24-47 vs 28-71 events per 100 patient-years, respectively). In the first 6 months, the fatigue AE incidence in the ENZA arms was slightly higher vs the control arms (26% vs 30% and 17% vs 28%, respectively). Time to fatigue onset in the ENZA and control arms was similar. In all trials, younger men (<75 years) experienced less fatigue vs older men (20% vs 35% vs 21% vs 42%, respectively), regardless of treatment.

Conclusions: Early-onset fatigue occurred slightly more frequently in ENZA-treated patients. Irrespective of treatment, fatigue was more common in men ≥75 years and was grade 3 in a small percentage of men.

Legal entity responsible for the study: Astellas Pharma, Inc. and Medivation, Inc.

Funding: Astellas Pharma, Inc. and Medivation Inc.


Table: 740P

<table>
<thead>
<tr>
<th>AEs, %</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>100</td>
<td>99.8</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>56</td>
<td>53</td>
</tr>
<tr>
<td>Back pain</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>17</td>
<td>16</td>
</tr>
</tbody>
</table>

Conclusions: 41 of 546 pts continued long-term AA + P (≥4 yrs), and no new safety signals were associated with prolonged treatment with AA + P. No Pts on LT AA + P may progress but have excellent survival and manageable toxicity.

Clinical trial identification: Clinicaltrials.gov NCT00887198

Legal entity responsible for the study: This study was sponsored by Jansen Research & Development (formerly Ortho Biotech Oncology Research & Development, unit of Sanofi Biogenica).

Funding: This study was sponsored by Jansen Research & Development (formerly Ortho Biotech Oncology Research & Development, unit of Sanofi Biogenica).


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Background: Fatigue is the most common and distressing symptom of which cancer-related fatigue (CRF) in CRPC. The VITAL study examines the prevalence and intensity of cancer-related fatigue (CRF) in CRPC.

Methods: cross-sectional study of CRPC patients including chemo-naïve metastatic (mCRPC) or high risk mCRPC (PSADT ≤10mo) in routine clinical practice. Fatigue and Quality of Life (QoL) data were collected using validated patient self-reported questionnaires(BFI-SF and FACT-G/P). Fatigue correlation with both patient and Quality of Life data were collected using validated patient self-reported questionnaires (BFI-SF and FACT-G/P).

Results: 235 patients were recruited (Jan-Sept 2015). Median age: 75.1 (46.2-92.4), median PSA: 17.8 ng/ml (0-2000), metastatic disease: 68.6%, EUROC 0-1: 90.6%. There was a high prevalence of fatigue (M1:73.9%; M0: 74.3%), with 38.3% of the patients having moderate or severe fatigue. High concordance existed between fatigue physicians and patient’s perception (Kappa index: 0.818). Cardiovascular and respiratory disorders were associated with an increase of fatigue in the multivariate analysis (OR: 4.7 and 3.6 respectively, p < 0.05). Mean FACT-G/P total score worsened once fatigue intensity increases (BFI item 3) (p < 0.001, table1). Focusing in mCRPC chemo-naïve we found differences in fatigue and QoL according to treatment. Patients receiving Abiraterone (AA) showed better FACT-P total score (Mean [SD]; AA: 119.9 [18.9], others: 103.3[23.1] p = 0.022) and less fatigue interference (BFI item 4 Mean [SD]; AA: 2.5 [2.3], others: 3.2[2.8] p = 0.045).
Conclusions: Our data show a high prevalence and intensity of fatigue and impact in QoL in chemo-naïve CRPC patients. The study highlights the relevance of fatigue awareness and its management in CRPC patients. Table.

Legal entity responsible for the study: Janssen-Cilag, Spain
Funding: Janssen-Cilag, Spain
Disclosure: All authors have declared no conflicts of interest.

Clinical outcomes and testosterone levels following continuous and intermittent androgen deprivation (CAD) in patients with relapsing or locally advanced prostate cancer (PC): A post hoc analysis of the IECAL study

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Background: IECAL is a large multicentre EU study evaluating similar efficacy, tolerability and QoL with CAD and intermittent androgen deprivation (IAD) with leuprolpen (Eligard®) in non-metastatic PC. This post hoc analysis investigated if patients (pts) achieving serum testosterone (T) levels ≤20 ng/dL within the 1st year of CAD have improved cause-specific survival (CSS) and time to PSA (castrate-resistant prostate cancer (CRPC)) progression.

Methods: Pts with locally advanced or relapsing non-metastatic PC following radical prostatectomy or radiotherapy were enrolled in this prospective, phase IIIB, open-label, randomised study (NCT03073690). After a 6-month induction with leuprolpen (Eligard®) 3-month depot 22.5 mg (plus bicalutamide 50 mg/day for 1 month), pts with PSA levels ≤1 ng/mL were randomised 1:1 to CAD (n = 361) or IAD (n = 340) with leuprolpen (Eligard®) for 36 months. Pts receiving CAD therapy were stratified by min, median and max T levels achieved during the 1st year of therapy into ≤20, 20-50 and >50 ng/dL subgroups. CSS and time to PSA (CRPC) progression were analysed by Kaplan-Meier analyses and Cox proportional hazards regression model.

Results: A total of 90.1%, 83.5% and 74.5% of pts receiving CAD achieved minimum, median and maximum serum T levels of ≤20 ng/dL, respectively. CSS rates and time to PSA progression did not differ significantly between T subgroups (table). Table: 741P

Conclusions: In pts receiving CAD, CSS and time to PSA (CRPC) progression did not differ according to T levels in the 1st year of therapy. This finding may have been due, at least in part, to the effectiveness of leuprolpen (Eligard®) in lowering T, as maximum T levels ≤20 ng/dL were achieved in 75% of pts over the 1st year of CAD.

Legal entity responsible for the study: Astellas Pharma, Inc. and Medivation, Inc.
Funding: Astellas Pharma, Inc. and Medivation, Inc.
Disclosure: B. Tombal: Advisory board member: Astellas, Bayer, Medivation, Ferring, Amgen, Sanofi. Aventis: Corporate-sponsored research: Astellas, Bayer, Medivation, Ferring, Amgen, Sanofi Aventis. T.L. Tamme: Advisory board member: Astellas, Orion Pharma, Bayer. Corporate-sponsored research: Astellas, Orion Pharma, Medivation, Janssen-Cilag, Bayer, Ferring, Camurus AB. All other authors have declared no conflicts of interest.

Outcomes of metastatic castration-resistant prostate cancer (mCRPC) patients (pts) treated with different new agents (NAs) sequence in post-docetaxel (DOC) setting. An updated analysis from a multicenter Italian study


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Background: Abiraterone acetate (AA), cabazitaxel (CABA), and enzalutamide (ENZ) may prolong survival in mCRPC pts receiving 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 (Euro Urol. 2015;68:147-53). In the present study we updated the analysis with longer follow-up by and 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 NA sequences after DOC: new hormone agent (AA or ENZ) followed by CABA (NA > CABA), CABA followed by AA or ENZ (CABA > NA), one NA followed by the other NA (NA > NA).

Results: A consecutive series of 344 mCRPC pts, median age 71 yrs (43-91), with bone (86%), nodal (53%) or visceral (16%) met, was identified. All received NAs as 2nd and 3rd line after DOC. The outcomes by both treatment lines and NAs are detailed in the table.
Efficacy of cabazitaxel, abiraterone, enzalutamide and docetaxel sequence in men with metastatic castration-resistant prostate cancer (mCRPC) in real life practice: The multinational, retrospective, observational CATS study

Methods: Results of 562 consecutive mCRPC patients were retrospectively collected in 31 centers in 7 European countries from Jan 2011 to Jan 2016. Disease history and clinical characteristics at initiation of each therapy were collected. PSA response ≥ 50%, radiological or clinical progression-free survival (PFS) and overall survival (OS) with each treatment sequence were evaluated.

Results: At sequence initiation, patient characteristics were similar between the 3 sequences: median age was 67 years, 95% were ECOG 0-1, 59% had high disease volume, 42.6% had pain and 8% had visceral metastases. Median number of D cycles was 6 in the 3 groups. Median numbers of C cycles were 7, 6 and 5 in groups 1, 2 and 3 respectively. Median duration of follow-up was 33.7, 31.1, and 23.7 months in groups 1, 2 and 3. Main results are provided in the table.

Table: 744P

<table>
<thead>
<tr>
<th>Sequence</th>
<th>PSA response ≥50%</th>
<th>OS from clinical PFS</th>
<th>Treatment 1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>D -&gt; C &gt; ART (n = 129)</td>
<td>61% / 11.5</td>
<td>37.3 / 32.4, 45.2</td>
<td>Treatment 1</td>
</tr>
<tr>
<td>D -&gt; ART &gt; C (n = 390)</td>
<td>63% / 11.9</td>
<td>38% / 11.3</td>
<td>36.0 / 33.4, 39.7</td>
</tr>
<tr>
<td>ART -&gt; D &gt; C (n = 41)</td>
<td>62% / 7.4</td>
<td>31% / 8.9</td>
<td>30.1 / 24.3, 52.7</td>
</tr>
</tbody>
</table>

*p value

Treatment 1: Docetaxel, Treatment 2: Cabazitaxel, Treatment 3: Abiraterone, Treatment 4: Enzalutamide.

Conclusions: PSA responses were generally similar for each treatment line in the 3 groups. No significant difference in OS was observed between the 3 sequences in this retrospective study. D showed a longer radiological or clinical PFS when given in first line. The activity of C was not influenced by ART. Sequencing should be based on individual disease characteristics and patients’ status and preference.

Legal entity responsible for the study: Sponsor ARTIC.

Funding: Sanofi and Janssen.

Disclosure: A. Angeleri: Consulting fee Sanofi; Travel for meeting Sanellas and Janssen. O. Caffo: Speakers bureaus: Astellas, Janssen, Sanofi, Bayer. S. Le Marchal: None.

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1. Sanofi France.


1. Bayer.

1. Janssen.

1. Roche.

1. Pharmamar.

1. Novartis.

1. Astellas, Ipsen, Jansen, Ferring, Bayer. J. Alexandre: Consulting fees (or other payment).

1. Roche, Novartis. S. Oudard: Consulting fees (or other payment). Sanofi, Bayer, Astellas, Janssen. All other authors have declared no conflicts of interest.

Treatment options in advanced castration-resistant, docetaxel-resistant prostate cancer (ACD-RPRO), Final results of a network meta-analysis

Methods: An indirect comparison of the efficacy of abiraterone, enzalutamide, cabazitaxel and Ra-223 was performed. The indirect comparison and the network meta-analysis were performed on data extracted from abiraterone, enzalutamide and Ra-223 vs placebo, and cabazitaxel vs mitoxantrone-prednisone comparisons in the treatment of ACD-RPRO. Overall Survival (OS) was the primary end point, Time to PSA progression (TTP-PSA) the secondary one. The results of indirect comparisons were reported as Hazard Ratio and 95% Confidence Interval, assuming an alpha error of 5% as index of statistical significance.

Results: The outcome of 4070 patients were analyzed. 378 were treated with cabazitaxel, 797 with abiraterone, 800 with enzalutamide, 614 with Ra-223, 377 with mitoxantrone and 1104 with placebo. No significant differences were observed for OS in all the indirect comparisons, while a significant improve in favor of enzalutamide was observed in TTP-PSA when compared with cabazitaxel, abiraterone or Ra-223, as detailed in the table.

Table: 745P

<table>
<thead>
<tr>
<th>Treatment (Y vs X)</th>
<th>OS (Y vs X)</th>
<th>TTP(PSA) (Y vs X)</th>
<th>Cabazitaxel (X)</th>
<th>Enzalutamide (X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ra-223 (X)</td>
<td>0.866 (0.672-1.167)</td>
<td>0.861 (0.615-1.205)</td>
<td>1.107 (0.827-1.482)</td>
<td></td>
</tr>
<tr>
<td>Abiraterone (Y)</td>
<td>0.87 (0.641-1.149)</td>
<td>0.784 (0.584-1.084)</td>
<td>0.784 (0.598-1.028)</td>
<td></td>
</tr>
<tr>
<td>Enzalutamide (Y)</td>
<td>0.984 (0.779-1.290)</td>
<td>0.784 (0.598-1.028)</td>
<td>2.339 (1.73-3.161)*</td>
<td></td>
</tr>
<tr>
<td>Cabazitaxel (Y)</td>
<td>0.338 (0.286-0.526)*</td>
<td>0.335 (0.262-0.429)*</td>
<td>1.156 (0.918-1.457)</td>
<td></td>
</tr>
<tr>
<td>Ra-223 (X)</td>
<td>0.906 (0.679-1.209)</td>
<td>0.784 (0.598-1.028)</td>
<td>2.339 (1.73-3.161)*</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Abiraterone, enzalutamide, cabazitaxel and Ra-223 can be considered comparable in terms of OS in ACD-RPRO, while enzalutamide seems to be superior in terms of TTP-PSA when compared with all the other comparators. On the basis of these data, the better safety profile, the patient’s compliance or pharmacoeconomic considerations should guide clinicians in daily clinical practice.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
Results: Median follow-up at database close was 14.2 months (range: 0.2-28.6). Mean age at enrolment was 72.6 years. 55% of patients had a Gleason score ≥ 8 at diagnosis. 58.8% of patients had comorbidities at enrolment, most commonly cardiovascular disorders (51.7%, 41.3% hypertension) and diabetes (15.2%). 87% patients (63.8%) were chemotheraphy-naïve at enrolment. During the 12-month observation period, 1191 patients (86.7%) initiated new mCRPC treatment. Descriptive, non-comparative data on previous treatment lines and time to next therapy by first documented treatment received on study are in the table.

Conclusions: The results provide unique insights into treatment and outcomes in a large, real-world mCRPC patient population. These older patients have a high prevalence of comorbidities that are common in clinical practice but often not taken into account in the results of interventional clinical trials. Follow-up of these patients will allow assessment of treatment patterns and outcomes, and thereby contribute to optimising outcomes in subsets of mCRPC patients in clinical practice.

Clinical trial identification: ClinicalTrials.gov NCT02236637

Legal entity responsible for the study: Janssen Pharmaceutical

Funding: Janssen Pharmaceutical


Follow-up method: a %; mean interval every x months (range) b 831 factors for 277 patients (Up to 3 factors/patient).

Global treatment patterns for late-stage prostate cancer: Updated results from ASPIRE-PCA


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Background: ASPIRE-PCA is an observational study that aims to describe the pattern of care for men with late-stage prostate cancer (PC). 1200 patients (pts) from the Americas, Europe, Asia, and the Middle East/North Africa are targeted for enrolment. We present updated data from December 2015.

Methods: Men with prostate adenocarcinoma enrol at the diagnosis of: biochemical failure after curative-intent therapy with a prostate-specific antigen (PSA) doubling time of ≤1 year; castration-resistant PC (CRPC), or metastatic PC (mPC) at initial presentation. Initial treatment decision and planned follow-up data were collected.

Results: 507 pts have enrolled from 72 sites in 21 countries: Americas, n = 53; Europe, n = 172; Asia, n = 271; and the Middle East/North Africa, n = 11. Biochemical failure, n = 90 (18%); CRPC, n = 181 (36%); mPC, n = 235 (46%); and missing, n = 1 (1%). Initial treatment decision and planned follow-up data are available for 277 pts. Androgen deprivation therapy (ADT) was the treatment of choice, with disease status being the primary driver of treatment selection (table). Initial ADT data are available for 223 pts. A gonadotropins-releasing hormone (GnRH) agonist with anti-androgen (aa) for flare protection only, was the most selected ADT. This combination was used for total androgen blockade in 4 CRPC and 6 mPC pts. The most common GnRH agonist, aa, and 2nd-generation androgen-directed therapy were: leuprolide, n = 106 (48%); bicalutamide, n = 108 (48%), and abiraterone, n = 17 (8%), respectively (sum >100%, as >1 option/pt). Enzalutamide was less frequently chosen (n = 7; 3%). The most favoured follow-up was PSA testing every 3 months. Updated regional differences will be presented.

Table: 746P

<table>
<thead>
<tr>
<th>Treatment</th>
<th>New treatment, n (%)</th>
<th>Androgen-deprivation therapy</th>
<th>Chemotherapy, immunotherapy, targeted therapy</th>
<th>Salvage radiotherapy</th>
<th>Androgen-deprivation therapy, n (%)</th>
<th>GnRH agonist and anti-androgen</th>
<th>GnRH agonist alone</th>
<th>Anti-androgen alone</th>
<th>2nd-generation androgen-directed therapy</th>
<th>Treatment missing</th>
<th>GnRH antagonist alone</th>
<th>GnRH antagonist and anti-androgen</th>
<th>GnRH agonist and 2nd generation androgen-directed therapy</th>
<th>Oestrogens</th>
<th>Most important factor for treatment selection, n (%)</th>
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<td>223 (100%)</td>
<td>90 (40%)</td>
<td>67 (30%)</td>
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<td>25 (11%)</td>
<td>7 (3%)</td>
<td>4 (2%)</td>
<td>2 (1%)</td>
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<td>2 (10%)</td>
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</tr>
</tbody>
</table>

Androgen-deprivation therapy

Chemotherapy, immunotherapy, targeted therapy

Salvage radiotherapy

Androgen-deprivation therapy

GnRH agonist and anti-androgen

GnRH agonist alone

Anti-androgen alone

2nd-generation androgen-directed therapy

Treatment missing

GnRH antagonist alone

GnRH antagonist and anti-androgen

GnRH agonist and 2nd generation androgen-directed therapy

Oestrogens

Most important factor for treatment selection

(%) Disease status: 239 (29%); Efficacy data from literature: 131 (16%); Performance status: 109 (13%); Efficacy data from own experience: 82 (10%); Age: 60 (7%); Comorbidities: 49 (6%); Prior therapy: 49 (6%); Prior response: 46 (6%); Preference/request: 40 (5%); Insurance/cost: 19 (2%); Other: 7 (<1%)

Follow-up method, n (%); mean interval every x months (range) PSA: 277 (253%) Clinical exam: 235 (85%), 2.9 (1-6) Radiography: 192 (60%), 5.9 (3-12)

*Sum >100% (>1 option/patient); b831 factors for 277 patients (Up to 3 factors/patient). GnRH, gonadotropins-releasing hormone; PSA, protein-specific antigen.
Switch from abiraterone + prednisone to abiraterone + dexamethasone after PSA progression under abiraterone + prednisone in asymptomatic metastatic castration-resistant prostate cancer (mCRPC) patients

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Background: Abiraterone acetate (AA) is active in mCRPC. AA is usually administrated with prednisone (P) to prevent mineralocorticoid excess until radiological or symptomatic progression of PSA. A switch from P to dexamethasone (D) was reported to induce tumor responses in patients progressing on AA + P. This prospective study was designed to evaluate the outcome of patients progressing on AA + P (< 0.2 ng/ml; time to PSA progression on AA + P) after the switch, and to determine predictive factors of switch efficiency.

Methods: Among 120 pts treated with AA between Jan 2013 and Apr 2016 in our institution, 48 consecutive asymptomatic mCRPC pts, progressing only biologically on AA + P were switched to AA + D. The median follow-up was 15.3 months.

Results: Median age at switching was 82 ± 7 years (57–92). Median time of hormonosensitivity was 82 months (mo). 7 pts previously received docetaxel. Median time to PSA progression on AA + P was 8.6 mo. Median (median) follow-up time from institution, 48 consecutive asymptomatic mCRPC pts, progressing only biologically on AA + P was matched daily, were switched to AA + D (3.05 ± 1.56 mo at the time of PSA increase. AA + D was administered until radiological and/or symptomatic progression.

Conclusions: Switch from P to D is able to reverse biological resistance to AA + P in almost half of mCRPC pts. Lasting PFS have been observed in pts with previous long hormonosensitivity and/or low PSA level and/or short time to PSA progression on AA + P. This switch deserves further evaluation in randomized studies.

Disclosure: Legal entity responsible for the study: Institut Mutualiste Montsouris Funding: Institut Mutualiste Montsouris

Efficacy and safety of enzalutamide (ENZ) vs placebo (PL) in chemotherapy-naïve patients (pts) with progressive metastatic castration-resistant prostate cancer (mCRPC) following androgen deprivation therapy (ADT): An Asian multinational study

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Background: In PREVAIL, pts with progressive mCRPC following ADT had significantly improved radiographic progression-free survival (PFS) and overall survival (OS) on ENZ vs PL (Beer TM et al, N Engl J Med, 2014). In the current study, the efficacy and safety of ENZ vs PL were evaluated in a similar patient population in China, Taiwan, Hong Kong and South Korea.

Methods: Pts with asymptomatic/mildly symptomatic progressive mCRPC following ADT were randomised 1:1 to ENZ (160 mg/day) or PL. The primary endpoint was time to prostate-specific antigen (PSA) progression (time from randomisation to PSA progression or death). The secondary endpoints were OS (time from randomisation to death) and rPFS (time from randomisation to radiographic progression). An interim analysis was planned following 169 PSA progression events. The unstratified Cox proportional hazards model (covariate = treatment group) and log-rank test (2-sided significance level = 0.011, primary: 0.05, secondary) were used. Safety was assessed by recording adverse events (AE).

Results: 409 pts from 49 centres were randomised (209 ENZ, 200 PL). Baseline characteristics were balanced between treatment groups. 169 PSA progression events occurred. Median time to PSA progression was 7.5 months in the ENZ arm vs 2.9 for PL (HR 0.36; 95% CI 0.27; 0.50; p < 0.0001). Median OS was not yet reached (NTR). Current results show a reduced risk of death in the ENZ arm vs PL (HR 0.35; 95% CI 0.17; 0.70; p < 0.0021). Median time to radiographic progression was also NTR for ENZ but was 4.7 months for PL (HR 0.28; 95% CI 0.19; 0.42; p < 0.001). The median time on treatment was 6.6 months for ENZ and 3.7 for PL. Although slightly more ENZ pts received 4 (1 treatment) + 5 TEAE (coste), 84.7% vs 80.5%, more pts in the PL arm reported at least 1 serious TEAE, 17.2% vs 24.5%; grade ≥3 TEAE, 24.4% vs 29.5% and TEAE leading to discontinuation, 12.9% vs 17%. No seizures or convulsions were reported in either arm.

Conclusions: ENZ showed significantly improved time to PSA progression over PL and was generally well tolerated. The trial was stopped as it had reached its primary objective.

Clinical trial identification: ClinicalTrials.gov NCT02394461. First received: November 13, 2014; Last updated: November 25, 2015

Legal entity responsible for the study: Astellas Pharma, Inc.

Funding: Astellas Pharma, Inc. and Medivation, Inc.

Disclosures: Y. Su. The author discloses that they received funding from Astellas Pharma Inc. for clinical studies. S. Yamada, S. Noda. The author declares that they own stocks in, and are an employee of, Astellas Pharma Inc. All other authors have declared no conflicts of interest.

Radium-223 with concomitant bone-targeting agents in metastatic castration-resistant prostate cancer (CRPC) patients treated in an international early access program (EAP)

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Background: The bone-targeting agents (BTAs) denosumab and bisphosphonates (BPs) are widely used in the supportive care of patients (pts) with CRPC and bone metastases. We present data on pts treated with radium-223 dichloride (Ra-223) with or without a concomitant BTA in an international EAP.

Methods: This was a prospective single-arm phase IIb study of CRPC pts with symptomatic or asymptomatic bone metastases (no visceral disease) recruited from 14 countries. Pts received Ra-223 50 kBq/kg [55 kBq/kg after NIST update] (iv injection) every 4 weeks for 6 cycles. Co-primary endpoints were safety and overall survival (OS). Exploratory analyses investigated the effects of concomitant denosumab (no BPs) or BPs (no denosumab) on OS and symptomatic skeletal events (SSE).

Results: 696 pts received at least one Ra-223 cycle. Of those, 127 (18%) pts were treated with concomitant denosumab (no BPs) and 435 (63%) without concomitant BTAs. Key baseline characteristics are reported in pts treated with Ra-223 with or without a concomitant BTA (Table). Median OS (moS) and median time to first SSE (mSSE) were longer in pts treated with Ra-223 and denosumab versus pts without a concomitant BTA (Table). While key baseline characteristics in pts treated with Ra-223 and denosumab were similar to pts treated with Ra-223 and BPs (no denosumab, 125 (18%) of 696), adding BPs to Ra-223 did not appear to improve mSSE. However, mSSE was prolonged in pts receiving Ra-223 and BPs versus pts who received Ra-223 without a concomitant BTA (Table).
Changes in alkaline phosphatase (ALP) dynamics and overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients treated with radium-223 in an international early access program (EAP)

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7 Department of Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy
8 Biostatistics, Modular Informatics LLC, New York, NY, USA
9 Pharmaceutical Division, Bayer, Whippany, NJ, USA
10 Department of Oncology-Pathology, Karolinska University Hospital, Stockholm, Sweden
11 Department of Surgery, University of Montreal Hospital Center, Montreal, QC, Canada

Background: Identifying a reliable marker of efficacy for radium-223 dichloride (Ra-223) would aid in the clinical management of mCRPC patients (pts). In exploratory analyses of mCRPC pts with symptomatic bone metastases treated with Ra-223 in the ALSYMPCA trial, OS was significantly longer in pts with a confirmed decline in ALP levels from baseline to week 12, compared with pts without a confirmed ALP decline. Here, we present data on ALP dynamics and OS and time to first symptomatic skeletal event (SSE) in pts treated with Ra-223 in an international EAP.

Methods: This was a prospective single-arm phase IIb study of CRPC pts with symptomatic or asymptomatic bone metastases (no visceral disease) recruited from 14 countries. Pts received Ra-223 50 kBq/kg (55 kBq/kg after NIST update) iv, every 4 weeks for up to 6 cycles. Co-primary endpoints were safety and OS. Explorer analyses investigated whether a confirmed decline (any magnitude) in ALP levels was associated with OS and time to first SSE.

Results: 696 pts received at least one Ra-223 cycle. Of those, 398 (57%) pts had a confirmed decline in ALP and 298 (43%) had no confirmed ALP decline. Key baseline characteristics are shown (Table). More pts with a confirmed ALP decline (374, 94%) received 5–6 Ra-223 injections than those with no ALP decline (99, 33%). Hazard ratios (HR) for confirmed ALP decline at week 12 on OS decline suggest a strong association of ALP decline with both longer OS (HR 0.299, 95% CI 0.227–0.395) and longer time to first SSE (HR 0.474, 95% CI 0.340–0.662) (Table).

Conclusions: In this EAP, pts treated with Ra-223 and a concomitant BTA appeared to have longer time to first SSE than those treated without a concomitant BTA. However, improvement in OS with a BTA was observed with denosumab but not with BPs. Prospective randomized controlled studies are required to confirm the benefit of this specific treatment combination in metastatic CRPC.

Clinical trial identification: ClinicalTrials.gov NCT01618370

Legal entity responsible for the study: Pharmaceutical Division of Bayer

Funding: Pharmaceutical Division of Bayer


NRA = not reached/available. *Measured from the brief pain inventory short form. Calculated from Cox proportional hazards model.
Radium-223 re-treatment from an international, prospective, open-label study in patients with castration-resistant prostate cancer and bone metastases


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Background: Radium-223 (Ra-223) 38 kBq/kg IV (55 kBq/kg after NIST update) is indicated in symptomatic bone-metastatic castration-resistant prostate cancer (mCRPC) patients (pts) with no visceral metastases (mets). In an international prospective trial in mCRPC pts (NCT01934790), Ra-223 re-treatment was allowed after initial 6 inj was well tolerated with very low radio bone progression rates (Sartor AS GO 2016). Reported are safety and total alkaline phosphatase (ALP) and prostate-specific antigen (PSA) dynamics.

Methods: All pts had CRPC with bone mets and completed 6 Ra-223 inj with no bone progression during that initial tx. Pts had radiologic or clinical progression after initial Ra-223 tx, and adequate hematologic (heme) values. Pts who started subsequent re-tx had radiologic or clinical progression after initial tx. Pts with grade 2 or 3 post-ts pts who started subsequent tx, and adequate hematologic (heme) values. Pts who started subsequent re-tx had radiologic or clinical progression after initial tx. Pts had radiologic or clinical progression after initial 6 Ra-223 inj, and adequate hematologic (heme) values. Pts who started subsequent re-tx had radiologic or clinical progression after initial tx.

Results: Of 44 Ra-223 re-tx pts, 29 (66%) received all 6 inj. Median time from last inj of Ra-223 tx was 6 mo. There were no marked alterations in ts adverse event (TEAE) incidence vs ALSYMPCA (Table) and no grade 4 or 5 heme TEAEs. 3 (7%) re-tx pts had grade 3 or 4 related TEAEs. Maximum follow-up times for ALP and PSA progression were 12.8 and 11.4 mo, respectively. Median time to ALP progression was not reached. Median time to PSA progression was 2 mo. ALP and PSA response rates at wk 12, 24, and any time before database cutoff are reported (Table).

Conclusions: Ra-223 re-tx was well tolerated, with minimal heme toxicity and ALP and PSA profiles similar to those of ALSYMPCA.

Clinical trial identification: NCT01934790

Legal entity responsible for the study: Pharmaceuticals Division of Bayer

Funding: Pharmaceuticals Division of Bayer

Disclosure: O. Sartor: Consultant or advisory role for Astellas, Bayer, Genentech, and Pfizer. V. Wagner: Was employed by Merck; is now employed by Bayer; stock or other ownership in Bayer. J. Garcia-Vargas: Employed by Bayer; travel, accommodations, expenses from Bayer. B. Mellado: Speaker for Astellas, Bayer; honoraria from Astellas. J. Domenec: Speaker for Bayer. J. Simon: Consultant or advisory role for Pfizer, Bayer, and Shire. M. Ochoa de Olza: Consultant or advisory role for Pfizer, Bayer, and Shire. A. Peer: Consultant or advisory role for Bayer, Johnson & Johnson, and Amgen. J. Garcia-Vargas: Consultant or advisory role for Bayer, Johnson & Johnson, and Amgen. J. Simon: Consultant or advisory role for Pfizer. P. Begues: Consultant or advisory role for Astellas, Bayer, and Shire. J. Duran: Consultant or advisory role for Bayer, Johnson & Johnson, and Amgen. J. Garcia-Vargas: Consultant or advisory role for Bayer, Johnson & Johnson, and Amgen.

Results: Of 44 Ra-223 re-tx pts, 29 (66%) received all 6 inj. Median time from last inj of Ra-223 tx was 6 mo. There were no marked alterations in ts adverse event (TEAE) incidence vs ALSYMPCA (Table) and no grade 4 or 5 heme TEAEs. 3 (7%) re-tx pts had grade 3 or 4 related TEAEs. Maximum follow-up times for ALP and PSA progression were 12.8 and 11.4 mo, respectively. Median time to ALP progression was not reached. Median time to PSA progression was 2 mo. ALP and PSA response rates at wk 12, 24, and any time before database cutoff are reported (Table).

ALP and PSA response rates (% decline from baseline).

Table 752P: Phase II study of weekly cabazitaxel for ‘unfit’ metastatic castration resistant prostate cancer patients (mCRPC) progressing after docetaxel (D) treatment. Circulating tumour cell (CTC) analysis (SOGUG-CABASEM Trial)

<table>
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<th>Re-tx Study,</th>
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<td>≥ 3 TEAE, %</td>
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</table>

Results: 75 pts have been enrolled. Median age was 73 y (range 54-85); 71 pts had ECOG 2, 84% had bone, 16% liver and 11% lung mets. Fourteen pts (34.3%) achieved ≥50% PSA response and 7 (17%) 50% response. Radiological response (PR) was observed in 4 pts (5%) and SD in 32 pts (45.7%). Median PSA PFS was 4.8 months and 12 weeks PSA PFS was 68.6%. Median OS was 12.6 months. Most frequent toxicities of all grades and grade 3-4 as % of pts were: anemia (80-17%), asthenia (54-19%), thrombocytopenia (20-10%), diarrhea (36-3%), nausea (27-1%), neutropenia (14-1%), peripheral neuropathy (19-0%), and anorexia (30-3%).
grade IV diarrhea or febrile neutropenia were observed. Nineteen of 32 pts (59%) had early CTC response. Results show a favorable association between early CTC response and PSA response (77% vs 53%) (p = 0.267), clinical benefit (RP + EE) (68% vs 31%) (p = 0.070), overall survival (15.8 m vs 7.2 m) (p = 0.175) and PSA PFS (7.8 m vs 3.1 m) (p = 0.094).

**Conclusions:** Our results suggest that weekly C plus P in unfit pts is an effective regimen with lower toxicity than the 3-weekly standard treatment. Early CTC response seems to be related with efficacy and could be of value as early efficacy endpoint.

**Clinical trial identification:** NCT01518828 / EudraCT 2011-004672-12

**Legal entity responsible for the study:** SOUGG (Spanish Oncology Genitourinary Group)

**Funding:** Sanofi

**Disclosure:** I. Duran: Consulting or advisory role: Amgen, Astellas, Roche-Genetech, Novartis, Janssen, Pierre-Fabre. Research funding: Sanofi, Janssen. All other authors have declared no conflicts of interest.

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**Table: 754P**

<table>
<thead>
<tr>
<th>Table: 754P</th>
<th>Prognostic Group</th>
<th>Description</th>
<th>N Median OS (months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>High</td>
<td>Hgb &lt; 11.3</td>
<td>177 12.4</td>
<td>REF</td>
<td>REF</td>
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<tr>
<td>2</td>
<td>High</td>
<td>Hgb &gt; 11.3 CICP &lt; 6.8</td>
<td>191 11.6</td>
<td>0.28 (0.22, 0.34)</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>High</td>
<td>Hgb &gt; 11.3 CICP &gt; 6.8 + Wnt</td>
<td>144 15.3</td>
<td>0.79 (0.63, 0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>4</td>
<td>High</td>
<td>Hgb &gt; 11.3 CICP &gt; 6.8 Wnt + pain &gt; 4</td>
<td>140 27.1</td>
<td>0.34 (0.27, 0.41)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>5</td>
<td>High</td>
<td>Hgb &gt; 11.3 CICP &lt; 6.8 + Wnt + pain &lt; 4</td>
<td>98 17.1</td>
<td>0.46 (0.33, 0.63)</td>
<td>0.003</td>
</tr>
<tr>
<td>6</td>
<td>High</td>
<td>Hgb &gt; 11.3 CICP &lt; 6.8 + Wnt + pain ≥ 4</td>
<td>17 11.4</td>
<td>0.68 (0.48, 0.95)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

**Conclusions:** Elevated serum levels of bone biomarkers are strongly associated with worse OS in CRPC. CART analysis incorporating bone biomarkers identified five distinct prognostic CRPC groups with differential OS outcomes. These results further define & establish the role of bone biomarkers in the design and conduct of CRPC clinical trials.

**Clinical trial identification:** ClinicalTrials.gov nct00134056; NCI SR01-C120469; CA180888 and CA180819

**Legal entity responsible for the study:** Southwest Oncology Group (SWOG) and the University of California Davis

**Funding:** National Cancer Institute (USA)

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**Neutropenia grade ≥ 3 during treatment with docetaxel (DOC) is associated with an improved overall survival (OS): A retrospective analysis of the TAX327 phase III trial**

A. Meisel1, D. Vogt2, R. de Wit3, J.S. de Bono4, O. Sartor5, M. Eisenberger6, F. Sterren-Liewen6

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**Background:** We previously showed that mCRPC patients developing grade ≥ 3 neutropenia (NP) with cabazitaxel had a prolonged progression-free survival (PFS) and OS (Meisel EJC 2016; 56:93-100). A risk model combining the neutropilo-to-lymphocyte ratio (NLR) and grade ≥ 3 NP was built to distinguish patients with a poor, intermediate and good prognosis.

**Methods:** The prospective phase III trial TAX327 randomly assigned (1:1:1) chemotherapy mCRPC patients to DOC (50 mg/m2) vs DOX (75 mg/m2) vs docetaxel + abiraterone. Hematology was collected before each cycle. Prophylactic G-CSF was allowed in case of febrile neutropenia. This post hoc analysis evaluates the influence of grade ≥ 3 NP and NLR on OS.

**Results:** OS in the DOC arms was significantly associated with the frequency of grade ≥ 3 NP (HR 1.95 [95% CI 1.81 – 2.10], p = 0.002). There was an even stronger association (HR 1.62 [95% CI 1.37 – 1.91], p = 0.001), when patients with at least one episode of grade ≥ 3 NP were analysed. Therefore we compared the OS of patients with multiple episodes of grade ≥ 3 NP to those with ≤ 1 episode of grade ≥ 3 NP and found a significantly prolonged OS for patients with multiple grade ≥ 3 NP episodes (HR 0.63 [95% CI 0.39 – 0.97], p = 0.016). The median OS was 17.1 months for patients with a single episode of grade ≥ 3 NP, 18.2 months for those without grade ≥ 3 NP and 22.8 months for those with multiple grade ≥ 3 NP episodes. The same association could be shown, when only the subgroup of patients treated with 3-weekly DOC, today’s standard first line chemotherapy, was considered (HR 0.64 [95% CI 0.38 – 0.92], p = 0.034). The hazard ratio effect was applicable for mCRPC patients treated with 14± day chemotherapy with DOC. The HR between risk category 0 (low NLR <1, grade ≥ 3 NP) and risk category 2 (high NLR ≥ 2, grade ≥ 3 NP) was 2.03 (95% CI 1.21 – 3.42), p = 0.007.

**Conclusions:** This post hoc analysis of TAX327 phase III trial suggests that the consecutive occurrence of grade ≥ 3 neutropenia with DOC is associated with an improved OS. Combining NLR and the occurrence of grade ≥ 3 neutropenia during taxane therapy may be useful to predict outcome.

**Legal entity responsible for the study:** Alexander Meisel & Frank Sterren

**Funding:** Sanofi

**Disclosure:** A. Meisel: Received Travel grants, advisory boards and honoraria from Sanofi.R. de Wit, J.S. de Bono, O. Sartor, M. Eisenberger: Advisory boards for Sanofi. Investigator: F. Sterren-Liewen. Received Travel grants, advisory boards and honoraria from Sanofi. Corporate sponsored research.All other authors have declared no conflicts of interest.

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**An innate immune response to intrinsic DNA damage predicts resistance to docetaxel in prostate cancer**

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**Background:** We have previously identified a molecular subtype in solid tumors which is characterised by STING mediated immune signalling due to abnormal DNA as a result of loss of DNA repair and immune checkpointing genes like PD-L1. This subtype is identified by a 44 gene signature expression signature, the DNA damage response deficient (DDR) assay. It is well recognised, that while loss of DNA repair can sensitize to DNA damaging chemotherapy, it may also confer resistance to anti-microtubule agents. We
hypothesized the DDRD positive molecular subtype in prostate cancer would confer a worse outcome following docetaxel treatment.

Methods: We used siRNA-mediated knockdown of DNA repair genes in DU145 cells to test for activation of the DDRD immune signal and sensitivity to docetaxel versus DNA damaging agents. We obtained FFPE diagnostic core biopsies from 52 men with Castrate Resistant Prostate Cancer (CRPC) treated with Docetaxel. Response to docetaxel was measured as a >50% decline in Prostate Specific Antigen (PSA).

Results: siRNA-mediated knockdown of BRCA1, BRCA2 and ATM resulted in increased resistance to docetaxel and increased sensitivity to cisplatin. Ten patients (19.2%) were DDRD positive and 42 (80.76%) were DDRD negative. 80% of DDRD positive and 47% of DDRD negative patients failed to benefit from docetaxel. DDRD positive tumour samples demonstrated an association with poorer overall survival post-docetaxel (HR 4.64, 95% CI 1.3 to 14.8; p = 0.0317, Median survival DDRD positive 12.14 months vs. DDRD negative 21.83 months).

Conclusions: The DDRD positive molecular subtype of prostate cancer, characterised by an immune response to DNA damage, has a reduced benefit from docetaxel. We intend to validate this observation in the STAMPede trial, investigating advanced prostate cancer patients who received docetaxel as primary therapy. These studies may lead to clinical trials where DDRD positive patients receive specific DNA damaging agents like carboplatin or an immune targeted therapy such as a PD-L1 inhibitor.

Legal entity responsible for the study: Queens University Belfast
Funding: Cancer Research UK
Disclosure: S. Walker: This Author is an employee of ALMAC diagnostics.

C. McCabe: Is an employee of ALMAC Diagnostics and her research is funded by Almac in part. L. Hill is an employee of ALMAC diagnostics and is funded by ALMAC.
R. Kennedy: Employee of Almac diagnostics. All other authors have declared no conflicts of interest.

### Table: 757P

<table>
<thead>
<tr>
<th>Subset</th>
<th>Phenotype</th>
<th>CRPC (%)</th>
<th>HV (%)</th>
<th>NLR (%)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>MDSC3</td>
<td>CD14+/+ CD15+/+</td>
<td>0.86</td>
<td>65</td>
<td>2.17</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>CD15+/+ CD33+/+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD14+ CD15+/+ CD62L+</td>
<td>5.76</td>
<td>65</td>
<td>5.16</td>
<td>0.373</td>
</tr>
<tr>
<td></td>
<td>CD15+/+ CD62L-/</td>
<td>1.99</td>
<td>65</td>
<td>0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>CD14+/+ CD33+/+ CD62L+</td>
<td>0.49</td>
<td>65</td>
<td>0.22</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>CD14+/+ CD33+/+</td>
<td>22.6</td>
<td>65</td>
<td>0.63</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td></td>
<td>CD15+ CD62L+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increased MDSCs were associated with 8q gain (MYC locus; MDSC8, N = 20 /57 evaluable, P = 0.004, MDSCA, 19 /55, p = 0.027), with BR1 loss (MDSC8A, N = 13 /56, P = 0.017), and with a lower likelihood of a PSA response (MDSC8A, P = 0.001).

Conclusions: MDSC subsets are increased in CRPC, with specifically granulocytic MDSC populations associated with molecular aberrations and treatment resistance.

Legal entity responsible for the study: Institute for Cancer Research, Johann de Bono
Funding: N/A
Disclosure: All authors have declared no conflicts of interest.

### 758P

**Neutrophil to lymphocyte ratio (NLR) impact on the survival and response duration of patients with metastatic castration resistant prostate cancer (mCRPC) treated with abiraterone acetate (AA)**

Medical Oncology, Centro Hospitalar Lisboa Norte - Hospital Sta Maria (FSTM-CHLN), Lisbon, Portugal

**Background:** The tumour microenvironment and inflammatory response are hallmarks of cancer progression. The NLR emerged as an indicator of the inflammatory state in patients with cancer, and has been negatively correlated with the prognosis of several solid tumors including mCRPC. The NLR is an available and easy to use tool and the authors assessed its role in the prognosis and response duration of patients treated with AA.

**Methods:** Retrospectively evaluated clinical data of patients with mCRPC from a single high volume center, with disease evaluable according to the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria, that underwent at least 12 weeks of AA. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count in the peripheral blood at baseline and at 12 weeks of treatment. NLR was stratified in two groups, > 5 and ≤ 5.

**Results:** 112 patients were treated with AA between 01/01/2013 and 31/12/2015, 90 for at least 12 weeks. The average NLR was 4.35 ± 3.07 (1.15-22.10). 33 had an NLR > 5 (36.7%), with both groups characteristics balanced. Median OS was 16.6 months in the NLR > 5 group and 27.7 months in the NLR ≤ 5 group (HR 0.507, p = 0.024). NLR remained predictive of a worse OS in a multivariate analysis that included pre-therapeutic prognostic factors. 21 patients (63.6%) with a NLR > 5 at baseline converted to ≤ 5 at 12 weeks of treatment with AA, and this was associated with a trend for a better OS (10.5 vs. 8.5 months, p = 0.197). Median PFS was 10.4 months in the NLR > 5 group and 9.7 months in the NLR ≤ 5 group (p = 0.867).

**Conclusions:** The NLR was prognostic in this analysis, with a NLR > 5 at baseline associated to a worse OS. There was no relation between NLR and response duration, with similar PFS in both groups. There was a trend for better OS in patients with a NLR > 5 at baseline that converted to ≤ 5 at 12 weeks of treatment with AA. Further studies are warranted to validate NLR as a prognostic tool with the use of AA.

Legal entity responsible for the study: Centro Hospitalar Lisboa Norte, Hospital de Santa Maria
Funding: Servicio de Oncología Médica, Centro Hospitalar Lisboa Norte, Hospital de Santa Maria
Disclosure: All authors have declared no conflicts of interest.

### Table: 757P

**Myeloid-derived suppressor cells (MDSCs) in metastatic castration-resistant prostate cancer (CRPC) patients (PTS)**

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**Background:** The relevance of targeting MDSCs in CRPC is increasingly recognized. Prognostical studies implicate MDSCs with senescence evasion, treatment resistance, loss of tumour suppressors (TSL) function or oncogene activation (OA). We investigated MDSC subsets in CRPC PTS with regard to their molecular underpinnings and associated with PSA response.

**Methods:** We prospectively evaluated MDSCs in 46 progressing CRPC PTS prior to new lines of therapy (n = 65), and in 14 male healthy volunteers (HV). Following blood draw MDSCs were analysed within 24 hours according to a gating strategy designed to standardize MDSC phenotyping. Here we report 5 MDSC subsets (phenotypes described in table), of which 2 are monocytic (MDSC3 and MDSC9), with Ge (MDSC8 and MDSCA) and 1 with a myeloid phenotype (MDSC1). Subsets are expressed as % of their parental population. Data were acquired with a BD Canto II with FACS-Diva and analysed using Kaluza 1.3. We tested for the association between MDSC subsets and copy number aberrations of 8q gain, loss (het/ homdel) of PTEN and RB1 in cell-free circulating DNA by targeted amplicon-based sequencing (IonTorrent) using CNVkit V0.3.5. Differences in levels of the 5 MDSC subsets were assessed using non-parametric testing (Mann-Whitney) and associations sequencing (IonTorrent) using CNVkit V0.3.5. Differences in levels of the 5 MDSC subsets were assessed using non-parametric testing (Mann-Whitney) and associations

**Results:** Overall, 65 baseline samples were analysed from 46 PTS with 4 of 5 MDSC subsets significantly increased in CRPC samples compared to HV (Table).

**Conclusions:** MDSC subsets are increased in CRPC, with specifically granulocytic MDSC populations associating with molecular aberrations and treatment resistance.
A post hoc analysis of radiographic progression with nonrising prostate-specific antigen in patients with metastatic castration-resistant prostate cancer (mCRPC) in the PREVAIL study


Oncology, Institut Gustave Roussy, Villejuif, France,9Medical Oncology, Royal Universitaires St. Luc, Brussels, Belgium,11Medical Affairs, Medivation, Inc., San Francisco, CA, USA,12Biostatistics, Medivation, Inc., San Francisco, CA, USA,

Medical Oncology, Astellas Pharma Global Development, Inc., Northbrook, IL, USA,13Biostatistics, Astellas Pharma, Inc., Leiden, Netherlands

Background: Advanced prostate cancer is a phenotypically diverse disease that evolves through multiple pathways. Prostate-specific antigen (PSA) level is the most widely used parameter for disease monitoring, but it has well-recognized limitations including discordant results when compared with imaging studies. We performed the first systematic quantification of patients (pts) with nonrising PSA (nrPSA) at a radiographic progression (RP) while on enzalutamide in the multinational, randomized controlled PREVAIL study.

Table: 760P

<table>
<thead>
<tr>
<th>Baseline parameter</th>
<th>Total score</th>
<th>Risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP &lt;105 U/L (Score = 0)</td>
<td>ALP ≥45 g/L (Score = 0)</td>
<td>ALB</td>
</tr>
<tr>
<td>PSA &lt;25 ng/ml (Score = 0)</td>
<td>ALP &lt;45 g/L (Score = 0)</td>
<td>ALB</td>
</tr>
<tr>
<td>PSA ≥25 ng/ml (Score = 1)</td>
<td>ALP ≥45 g/L (Score = 1)</td>
<td>ALB</td>
</tr>
<tr>
<td>ALP ≥105 U/L (Score = 2)</td>
<td>PSA ≥25 ng/ml (Score = 2)</td>
<td>ALB</td>
</tr>
<tr>
<td>PSA &lt;25 ng/ml (Score = 1)</td>
<td>ALP &lt;45 g/L (Score = 1)</td>
<td>ALB</td>
</tr>
<tr>
<td>PSA ≥25 ng/ml (Score = 1)</td>
<td>ALP ≥45 g/L (Score = 1)</td>
<td>ALB</td>
</tr>
</tbody>
</table>

Conclusion: Three baseline laboratory parameters defined risk groups in a classification system and explained differential clinical benefits for men in TERRAIN, including the ENZA-treated subgroup.

Legal entity responsible for the study: Astellas Pharma, Inc. and Medivation, Inc.

Funding: Astellas Pharma, Inc. and Medivation, Inc.

Disclosure: A. Armstrong: reports grants and personal fees from Medivation/Astellas, Janssen, Durker, Sanofi Aventis, Bayer.C.S. Higano: reports consultant or advisory role with Astellas, Medivation; research funding from Medivation; other from Astellas, Medivation.P. Iversen: reports funding from Astellas, Medivation during the conduct of the study; personal fees from Janssen, Ferring outside the submitted work.C. N. Sternberg: reports personal fees from Astellas, during the conduct of the study, personal fees from Johnson & Johnson, personal fees from Ipsen, personal fees from Bayer, personal fees from Millenium, outside the submitted work.D. E. Rathkopf: reports grants from Medivation, during the conduct of the study; grants from Janssen, Medivation, Millenium, Celgene, Novartis, Ferring, outside the submitted work.Y. Loriot: reports personal fees from Medivation, Astellas, Sanofi, Janssen, Oncogenex, Bayer, Ipsen, outside the submitted work.J. de Bono: reports personal fees from Astellas B. Tombal: reports grants, personal fees and non-financial support from Astellas, personal fees from Medivation personal fees from Bayer, grants and personal fees from Ferring, personal fees and grants from Sanofi, outside the submitted work.S. Abhyankar: reports personal fees from Medivation, during the conduct of the study; personal fees from Medivation, Inc, outside the submitted work.P. Lin: is a Medivation employee.A. Krivoshik: employee of Astellas and hold stock in Abbott and AbbVie.D. Phung: is an Astellas employee.T.M. Beer: reports grants from Astellas, Medivation, Janssen, during the conduct of the study, personal fees from Janssen Japan, Astellas, other from Medivation, Astellas to participate in a certified nursing education program, outside the submitted work.All other authors have declared no conflicts of interest.

761P

How should we treat castration-resistant prostate cancer patients who have received androgen deprivation therapy (ADT) plus docetaxel upfront for hormone-sensitive disease?

Mature analysis of the GETUG-AFU 15 phase III trial

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Background: Since 2015, docetaxel chemotherapy, combined with ADT, is considered the standard of care in fit men with metastatic hormone-naïve prostate cancer (mHNC), based on data from three phase III trials (GETUG-AFU 15, CHARACTED, and STAMPEDE). No data are currently available regarding activity of treatments used beyond progression after upfront ADT and docetaxel.

Methods: We retrospectively collected data from patients (pts) participating in the GETUG-AFU 15 phase III trial concerning treatments received beyond progression for castration-resistant disease (CRPC) in both arms (ADT + docetaxel).
including treatment efficacy (measured by a PSA decline, physician assessment of clinical benefit, and time to events), and toxicity (NCl-CTC grading).

Results: 245 pts received at least one anticancer treatment at CRPC progression. The toxicities most frequently used and their efficacy are detailed in the Table. Toxicity was mild, with only rare grade 3-4 events (17%). Median overall survival measurement after the onset of CRPC was respectively 2.29 years (IC95% [1.84-2.59]) and 1.97 years (IC95% [1.64-2.73]) in the ADT and ADT + D arms.

**Conclusion**: In this retrospective analysis, anti-cancer activity was suggested with androgen receptor axis-targeted agents even in patients with metastatic prostate cancer treated upfront with ADT + docetaxel. We observed that docetaxel challenge had rather limited activity in this setting.

**Clinical trial identification**: NCT00104751; release date: 2013 February (Lancet Oncol)

Legal entity responsible for the study: Unicancer

Funding: French Health Ministry and Institut National du Cancer (PHRC), Sanofi-Aventis, AstraZeneca, and Amapen

Disclosure: F. Joly: Roche, Pfizer, Novartis, Sanofi, Jansen, Astellas.M. Soulié: Agen

Background: Metabolic conditions (diabetes, obesity, or dyslipidemia) may be linked with prostate cancer (PCa) aggressiveness and death. The presence of these metabolic aberrations may enable us to identify those men who are at risk of early treatment failure. Here, we examine the effect of baseline metabolic aberrations on time to disease progression, prostate cancer specific and all cause death.

**Methods**: This study was conducted using a retrospective review of case report forms (CRF) of 2,817 men with locally advanced/metastatic hormone naive PCA commencing long term ADT who enrolled in the control arm of the STAMPEDE trial (ISRCTN78818544) between 2005 and 2015. Data on the following metabolic aberrations at baseline was included: hypertension (systolic blood pressure >140mmHg and/or diastolic blood pressure 90mmHg or confirmed history of hypertension), obesity (BMI >30kg/m²), dyslipidemia (HDL <1.0mmol/l) and impaired glycaemia (confirmed history of type 2 diabetes (T2DM)). Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals comparing patients with and without metabolic aberrations for risk of PCa progression and death.

**Results**: During a median follow up of 1.75 years those with three or more metabolic aberrations at baseline were more likely to have local progression (HR: 1.61, 95% CI 1.09-2.36) after adjusting for age, Gleason score, PSA, type of ADT and TNM stage. A similar trend was seen for metastatic progression (HR: 1.24, 95% CI 0.97-1.58).

**Conclusions**: Our findings suggest that baseline metabolic aberrations may be associated with earlier treatment failure. Thus identifying a higher risk patient group in which to intensify therapy including management of metabolic risk. Further prospective studies examining this association are required.

**Clinical trial identification**: EudraCT 2004-000193-31 (SRCTN78818544)
CARD: A randomized phase 4 trial comparing cabazitaxel and an androgen receptor (AR)-targeted agent in men with metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel and an alternative AR-targeted agent

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Background: mCRPC is highly heterogeneous with coexistence of AR-dependent and AR-independent tumor clones. New AR-targeted agents (abiraterone acetate, enzalutamide) and taxanes (docetaxel (DOC), cabazitaxel – specifically developed to overcome DOC resistance) are the backbone of mCRPC therapy. The rising concern of cross-resistance between mCRPC therapies and the evidence that some patients may not respond to all available drugs have increased the complexity of managing mCRPC. There is thus a need to design trials helping to define the optimal sequence of therapies to optimize patient outcomes.

Trial design: CARD is a randomized phase 4 trial involving 79 sites in 12 European countries. A total of 324 patients with mCRPC previously treated with DOC and who failed a prior AR-targeted agent (abiraterone acetate or enzalutamide, either before or after DOC) within 12 months of AR-targeted treatment initiation will be randomized (1:1) to receive cabazitaxel (25mg/m2 every 3 weeks plus daily prednisone and prophylactic G-CSF) or the alternative AR-targeted agent until radiographic progression, unacceptable toxicity or patient’s request. Randomization will be stratified by ECOG performance status (0–1 vs 2), time to progression with prior AR-targeted agent (>6 vs. 6–12 months) and timing of AR-targeted agent (before or after DOC). The primary endpoint is radiological progression-free survival (rPFS) as per PCWG2 definition (Scher, JCO 2008, 26:1148–1159). Secondary endpoints include overall survival, objective tumor response and its duration, PSA response, time to PSA progression/ radiographic progression/ pain progression/ first symptomatic skeletal event, quality of life (FACT-P), health status/utility (EQ-5D-5L), safety and the Epic Sciences CTC signature of resistance to AR-targeted agents. rPFS will be analyzed using 2-sided log-rank test adjusted for stratification factors. The trial has 90% power to detect a hazard ratio of 0.67, at a significance level of 0.05. Kaplan-Meier estimates/cures will be produced for both treatment groups. The CARD trial is currently recruiting.

Clinical trial identification: NCT02485656

Legal entity responsible for the study: Sanofi

Funding: Sanofi

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Efficacy and safety of enzalutamide plus androgen deprivation therapy vs placebo plus androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: the ongoing ARCHES trial

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Background: Androgen deprivation therapy (ADT) and docetaxel (DOC) chemotherapy are the preferred initial treatments for fit men with newly diagnosed metastatic prostate cancer (mPCa). Based on recent data from Phase 3 trials (STAMPEDE, CHAARTED), the concurrent use of combined androgen blockade antihormones (eg bicalutamide) may provide more-durable disease control than ADT alone, but the role of more-potent antihormone therapy in contemporary practice in the DOC chemotherapy setting is unknown. Enzalutamide (ENZA), a potent androgen...
ATLAS: A phase 3 trial evaluating the efficacy of apalutamide (ARN-509) in patients with high-risk localized or locally advanced prostate cancer receiving primary radiation therapy


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Background: Current management of high-risk localized or locally advanced prostate cancer includes 2 to 3 years of androgen deprivation therapy (ADT) and gonadotropin-releasing hormone agonist (GnRHa) along with primary radiation therapy (RT). Despite aggressive treatment, there is still a higher risk of metastasis and prostate cancer-related death in these patients. We hypothesize that the addition of the selective androgen receptor antagonist apalutamide to GnRHa will improve metastasis-free survival in high-risk patients receiving primary RT.

Trial design: This is a randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of apalutamide in patients with high-risk localized or locally advanced prostate cancer (Gleason score ≥ 8 and ≥ 2 T2c or a Gleason score of ≥ 7 and prostate-specific antigen ≥ 20 ng/mL and ≥ 2T2c) receiving primary RT. Randomization: Gleason score (7 or ≥ 8), NO or N1, brachytherapy boost (yes or no), and region (North American, European, or Other). All patients will receive active treatment with GnRHa throughout the 30 (28-day) treatment cycles. Randomization: 1:1 to apalutamide or control. Neoadjuvant/concurrent (cycles 1-14) to RT (74-80 Gy): apalutamide 240 mg/d and placebo. Primary endpoint: metastasis-free survival. Secondary endpoints: time to local-regional recurrence, time to castration-resistant disease, time to distant metastases, and overall survival. Imaging and bone scan will be conducted at baseline and then every 6 months following biochemical failure until documented distant metastases by blinded independent central review or death. Approximately 1500 patients will be accrued to provide appropriate statistical power to detect the hypothesized risk reduction (25%) in metastasis or death. An independent data monitoring committee is commissioned to review trial data. Approximately 300 study sites are planned in 20 countries across North America, Latin America, Europe, and Asia. Sites in 11 countries are currently recruiting.

Clinical trial identification: NCT02353161

Legal entity responsible for the study: Janssen Research & Development

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Disclosure: D. Dearealey: Consulting or Advisory Role - Cadence Research and Consulting, FirstWord, Janssen Pharmaceuticals, Janssen Pharmaceuticals, Sandor, and Takeda; Travel, Accommodations, Expenses - Takeda; Expert Testimony - Vitrail Life, Honoraria - Takeda; M. McKenzie: Honoraria - Amgen and Bayer; Consulting or Advisory Role - Johnson & Johnson; E. Baskin-Bey: Employee of Janssen Research & Development; R. Tyler, T. Kheoh, S. Thomas: Employee of Janssen Research & Development and holds stock in Johnson & Johnson; J. Melchior: Speaker and Investigator Fees - Janssen.S.J. Freedland: Consulting or Advisory Role - Astellas Pharma, Janssen Biotech, MDxHealth, Medivation, and Sanofi; Speakers’ Bureau - Medivation, Travel, Accommodations, Expenses - Myriad Genetics and Sanofi; A. Wilkirm: Employment - Sanofi; Honoraria - Astellas Pharma, Bayer, Janssen, and Sanofi; Consulting or Advisory Role - EXINI Diagnostics; A.P. Dicker: Consulting or Advisory role - Genview, Janssen, Merck, and Redhill.T. Wiegell: Honoraria - Ferring, Hexal, Ipsen, and Siemens; Consulting or Advisory Role - Ferrin and Ipsen.N. Shore: Consulting or Advisory Role - Astellas, Bayer, Ferring, Janssen, Millennium, Pfizer, and Sanofi; Research Funding - Carolina Urologic Research Center; Travel, Accommodations, Expenses - Astellas, Bayer, Ferring, Janssen, Millennium, Pfizer, and Sanofi.M. Smith: Consulting or Advisory Role - Astellas Pharma, Bayer, and Janssen Oncology; M. Yu: Employee of Janssen Research & Development and holds stock in Johnson & Johnson.H.M. Sandler: Consulting or Advising Role - Medivation or MDxHealth; Consultant for: Blue earth, Evi, Ferring, Janssen Pharmaceuticals, and Sanofi; Honoraria - Varian Medical Systems All other authors have declared no conflicts of interest.

Background: After radical prostatectomy or radiotherapy, about 1 of 4 men with adenocarcinoma of the prostate will develop a biochemical recurrence manifested by increasing levels of prostate-specific antigen (PSA). Of these, approximately 1 of 3 will eventually develop clinically detectable metastatic disease. To date, there is no approved therapeutic option for patients who have PSA relapse after surgery and/or radiotherapy and are at high risk for metastatic disease. Androgen deprivation is the facto standard and most commonly prescribed treatment in this setting. The EMBARK trial is designed to address this unmet need in high-risk, nonmetastatic, hormone-sensitive prostate cancer patients who recur after primary therapy.

Trial design: The EMBARK trial will randomize approximately 1860 subjects globally, across 200 international sites, into 3 treatment arms: leuprolide + enzalutamide, leuprolide + placebo and enzalutamide monotherapy. Enrollment is ongoing since Jan 2015. Subjects must fulfill the following entry criteria indicative of having biochemical failure and high-risk disease: PSA doubling time of ≥ 2.0 ng/mL for subjects who had prior radical prostatectomy or ≥ 3.0 ng/mL and ≥ 2 nadir + 2 x ng/mL for subjects who had radiotherapy as the primary therapy; androgen deprivation therapy ≤ 36 months in duration and ≥ 9 months before randomization and administered only in the neoadjuvant/adjuvant setting; no evidence of soft-tissue or bone metastases at the time of enrollment; and testosterone level > 150 ng/dL. In each arm, subjects will be evaluated every 12 weeks through the treatment course. Imaging studies with computed tomography/magnetic resonance imaging and bone scans will be performed every 25 weeks until the primary efficacy endpoint of metastasis-free survival is met. Subjects are allowed 1 treatment suspension (of the study drugs) at wk 37 if the PSA levels are < 0.2 ng/mL. Treatment will be reinitiated if PSA values rise ≥ 2.0 ng/mL for patients with prior prostatectomy or ≥ 5.0 ng/mL for those with only prior radiotherapy.

Clinical trial identification: NCT02319837

Legal entity responsible for the study: Medivation, Inc. and Astellas Pharma, Inc.

Funding: Medivation, Inc. and Astellas Pharma, Inc.


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TITAN: A randomized, double-blind, placebo-controlled, phase 3 trial of apalutamide (APN-509) plus androgen deprivation therapy (ADT) in metastatic hormone-sensitive prostate cancer (mHSPC)

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Background: There is an increased focus on improving outcomes of prostate cancer (PC) patients (pts) by introducing treatments before castration resistance occurs. Recent studies of NUTANITED (NCT02552394) and STAMPEDE (James Lancet. 2015) demonstrate a survival advantage with ADT (gonadotropin-releasing hormone analog or surgical castration) in combination with docetaxel (DOC) for pts with metastatic PC and practice guidelines recommend ADT + DOC for pts with metastatic disease. Inhibition of the androgen receptor (AR) in addition to ADT may provide more complete blockade of androgen signaling vs ADT alone. We hypothesize that apalutamide (APA), a selective AR antagonist, plus ADT will improve radiographic progression-free survival (rPFS) and overall survival (OS) compared with ADT alone, and have an acceptable safety profile in pts with mHSPC.

Trial design: This is a randomized, multicenter, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy and safety of APA + ADT in pts with Eastern Cooperative Oncology Group performance status ≤1 and mHSPC (metastatic disease documented by ≥1 bone lesions with or without visceral metastasis). Pts will be stratified by Gleason score (≤7 vs >7), region (North America, European Union vs ≤7), and prior DOC use (yes/no). Up to 6 cycles of DOC for mHSPC is allowed, with last dose within 2 mos of randomization. Up to 6 mos ADT for mHSPC is allowed prior to randomization. Approximately 1000 pts will be randomized (1:1) to APA (240 mg/d) + ADT or placebo + ADT in 28-day cycles. Co-primary end points: rPFS and OS. Secondary end points: time to pain progression, time to skeletal-related event, time to chronic opioid use, and time to initiation of cytokine chemotherapy. Samples for pharmacokinetics and biomarkers will be collected to correlate with clinical parameters. An independent data monitoring committee will review safety and efficacy data.

Clinical trial identification: NCT02449318
Legal entity responsible for the study: Janssen Global Services, LLC.
Funding: Janssen Global Services, LLC.
genitourinary tumours, non-prostate

**Axitinib in combination with pembrolizumab in patients (pts) with advanced renal cell carcinoma (aRCC): Preliminary safety and efficacy results**


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Background: Axitinib, an inhibitor of vascular endothelial growth factor receptors, is appropriate for patients with metastatic renal cell carcinoma. Pembrolizumab is a humanized monoclonal antibody that blocks binding of the immune-checkpoint receptor programmed death-1 (PD-1) to its ligands (PD-L1/2). Here we report preliminary safety and efficacy results from an ongoing phase Ib study of axitinib plus pembrolizumab in treatment-naive pts with aRCC.

Methods: Pts included have clear-cell aRCC with primary tumor resected, ≥2 measurable lesions, ECOG performance status 0–1, controlled hypertension, and no prior systemic therapy for aRCC. Axitinib is administered orally 5 mg twice daily; pembrolizumab is administered 2 mg/kg intravenously on Day 1 of each 3-week cycle. Tumors are assessed, using RECIST v1.1, at baseline, week 12, and every 6 weeks thereafter. Study endpoints include adverse events (AEs), other safety measures and tumor response. IHC-based assay was used to stain tumor cells for PD-L1 expression.

Results: As of March 1, 2016, 52 pts (79% male; 87% white; mean age 61 years) were enrolled. Eleven (21.2%) pts discontinued both treatments: disease progression (n = 4); treatment-emergent AEs (n ≥ 5); diarrhea, headache/joint pain, fatigue/joint pain, colitis/hepatitis, aggravated rheumatoid arthritis/poorisastis, and drug-induced liver injury; and other (n = 1). Thirty-five (67.3%) pts had objective response: 2 had complete response and 33 had partial responses. 11 pts had stable disease. For the 11 pts enrolled in the dose finding phase, 7 remained progression free at 11 months and the median PFS is not yet mature. Ten pts tested positive for PD-L1. Most common (≥2 pts) grade 3 AEs included hypertension (n = 10), diarrhea, headache, hyponatremia, alanine aminotransferase (ALT) increased, and aspartate aminotransferase (AST) increased (n = 3 each). Grade 4 AEs included dyspnea and hyperuricaemia (n = 1 each). Immune-related grade 3 AEs included ALT and AST (n = 2 each), and diarrhea and colitis (n = 1 each).

Conclusions: This preliminary analysis indicates axitinib plus pembrolizumab is well tolerated and exhibits antitumor activity in treatment-naive pts with aRCC.

Clinical trial identification: NCT02337427

Legal entity responsible for the study: Pfizer Inc

Funding: Pfizer Inc


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A phase I study of cabozantinib plus nivolumab (CaboNivo) in patients (pts) refractory metastatic renal cell carcinoma (mUC) and other genitourinary (GU) tumors

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Background: Cabo is a multiple receptor tyrosine kinase inhibitor primarily targeting MET and VEGFR2. Correlative studies support the theory that cabozantinib has immunomodulatory properties. Nivo is a monoclonal IgG4 antibody to PD-1. We report the safety and clinical activity of the combination of CaboNivo in pts with mUC and other GU tumors (NCT02496208).

Methods: This phase I trial used a rolling 6 design. 6 pts were treated at 4 dose levels (DL) for part I (CaboNivo) of the study. Pts received Cabo PO daily and Nivo IV q2wks: DL2 Cabo 40mg/Nivo 1mg/kg, DL3 Cabo 40mg/Nivo 3mg/kg, DL4 Cabo 60mg/Nivo 3mg/kg. Tumors were assessed for overall response rate (ORR) q8wks (RECIST 1.1). Adverse events (AEs) were graded (G) by NCI-CTCAE v4.0.

Results: From 7/22/15-5/11/16, 24pts (mUC N = 6; bladder urachal N = 4; bladder squamous cell carcinoma (SCC) N = 3; germ cell tumor (GCT) N = 5; castrate-resistant prostate cancer (CRPC) N = 4; renal cell carcinoma (RCC) N = 1, and trophoblastic tumor N = 1) were treated. Median age was 55 (range 35-75), 21 (88%) were male. 6 pts required dose reductions (N = 2 DL1; N = 1 DL2; N = 2 DL3; N = 4 DL4); for PPE G2 N = 3 (DL1/2/4); fatigue G1/2 N = 2 (DL3), diarrhea G2 N = 1 (DL3), lipase/amylose elevation G3 (DL3), weight loss G1 N = 1 (DL4), and anorexia/dehydration G2 N = 2 (DL4). Common treatment-related G1/2 AEs were transaminitis N = 20, diarrhea elevation G3 (DL4). Common treatment-related G1/2 AEs were transaminitis N = 20, diarrhea N = 11, hoarseness N = 7, dysgeusia N = 5, thrombocytopenia N = 5, hyponatremia N = 5. Grade 3 AEs included neutropenia N = 3 (DL1), fatigue N = 2 DL2, mucositis N = 1 (DL3), vomiting N = 1 (DL3), N = 1 (DL3). There were no G4/5 toxicities, no immune-related AEs and no DLTs. 18 pts were evaluable for response. ORR was 33% 6/18 (1 CR (bladder SCC), 5 PRs (mUC, RCC, urachal, urethral SCC, CRPC). All responses were ongoing at cutoff: SD 38% 7/18.

Conclusions: CaboNivo was well tolerated with no DLTs. Cabo 60mg resulted in more dose reductions due to clinically significant AEs. The recommended dose was Cabo40mg/Nivo3mg/kg. Part II of the phase 1 triplet with ipilimumab (CaboNivoIpi) is ongoing. Expansion studies in pts with mUC and RCC are planned.

Clinical trial identification: NCT02496208

Legal entity responsible for the study: N/A

Funding: NCI

Disclosure: All authors have declared no conflicts of interest.
Phase 1b dose-finding study of avelumab (anti-PD-L1) + axitinib in treatment-naive patients with advanced renal cell carcinoma

Background: Avelumab, a fully human IgG1 antibody that inhibits PD-L1. This ongoing phase 1b study (NCT02493751) evaluates safety and tolerability of avelumab + axitinib in treatment-naive pts with aRCC to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D).

Methods: Eligible pts have histologically confirmed aRCC with a clear-cell component, primary tumour resection, ≥2 measurable lesions, available tumour specimen, ECOG PS ≤1, and no prior systemic therapy for aRCC. MTD was estimated using the modified toxicity probability interval method, which determines the dose for future cohorts using all pts treated in prior and current cohorts. Adverse events (AEs) were graded by NCI-CTCAE v4.0. Objective response rate (ORR; RECIST v1.1) was evaluated.

Results: The starting dose was avelumab 10 mg/kg (1h IV infusion) Q2W + axitinib 5 mg PO BID. By 5 Apr 2016, 6 pts (median 59.5 yrs [range 45-73]) were treated with avelumab for a median of 17.6 wks (range 11.9-21.7) and axitinib for a median of 16.3 wks (range 12.7-22.7). One DLT of grade 3 proteinuria occurred. The most common treatment-related adverse events (TRAEs) of any grade were dysphonia and hypertension (n = 4 pts each) and fatigue and headache (n = 3 each). Grade 3-4 TRAEs occurred in 4 pts: hypertension (n = 2), palmar-plantar erythrodysesthesia syndrome (n = 1), lipase increased (n = 1), and proteinuria (n = 1). No pt discontinued due to a TRAE. Confirmed PR was observed in 5 pts (ORR 83.3%, 95% CI 39.5, 99.6) and stable disease in 1 pt with tumour shrinkage not meeting PR.

Conclusions: The combination of avelumab 10 mg/kg Q2W + axitinib 5 mg BID met MTD criteria and RP2D. Clinical benefit was observed in all 6 pts studied, with PR in 5 pts. Enrolment is ongoing in the expansion cohort. These results provide a rationale to investigate efficacy and safety of avelumab + axitinib vs current nontherapies for aRCC, including a pivotal, randomised phase 3 trial vs sunitinib that began in Mar 2016. *Proposed INN

Clinical trial identification: NCT02493751

Legal entity responsible for the study: N/A

Funding: Pfizer Inc.

Disclosure: B.I. Rini: Advisory Role: Pfizer, Roche, BMS, Acceleron, Novartis, GSK

Avelumab (MSB0010718C; anti-PD-L1) in patients with metastatic urothelial carcinoma progressed after platinum-based therapy or platinum ineligible

Background: Avelumab, a fully human IgG1 antibody that inhibits PD-L1. In a large phase 1b study (NCT01772094), avelumab showed preliminary safety and efficacy in a cohort of 44 patients (pts) with metastatic urothelial carcinoma (mUC) progressed after platinum-based chemotherapy or platinum ineligible. An additional cohort was enrolled to further characterise efficacy and safety of avelumab in mUC.

Methods: Eligible pts received avelumab 10 mg/kg (1h IV infusion) Q2W until confirmed progression, unacceptable toxicity, or withdrawal. Tumours were assessed every 6 wks (RECIST 1.1) and reviewed by an independent committee. Confirmed objective response rate (ORR) and progression-free survival (PFS) were evaluated.

Results: As of Jan 18, 2016, 129 pts were treated with avelumab, including 113 (87.6%) with disease progression after platinum-based therapy and 9 (7.0%) who were platinum ineligible. Primary tumour sites were bladder (74 pts, 57.4%), urethra (23 pts, 17.8%), renal pelvis (22 pts, 17.1%), and upper (8 pts, 6.2%). Median time from metastatic diagnosis was 10.7 mos. Pts had received a median of 2 prior lines (range, 0-6) for advanced disease. Median duration of treatment was 10.4 wks (range, 2-36). 78 pts (60.5%) had a treatment-related (TR) AE; most common (≥10%) were infusion-related
Quality of life (QoL) and neurotoxicity in germ-cell cancer survivors (GCCS)

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Background: The majority of patients with testicular cancer become long-term survivors. Hence, treatment is associated with late effects which may hamper QoL. The aims of the present study were to assess the impact of treatment on long-term QoL and evaluate the influence of neurotoxicity on QoL.

Methods: All GCCS identified in the Danish DaTeCa database were asked to fill in a questionnaire concerning late-effects Nov 2014 – Jan 2016. QoL was assessed with EORTC-QLQ C30 including 30 items divided into 15 subscales. Neurotoxicity was assessed with the FACT/GOG NTX12-scale including 12 items, divided into 4 subscales (neuropathy, ototoxicity, motor impairment, and dysphonia). Patients were divided into treatment groups; surveillance only (reference), n = 1092, radiotherapy (RT), n = 299, BEP chemotherapy (CT), n = 790, and more than one line of treatment (MTOL), n = 82. Outcomes were compared with ordinal logistic regression using treatment and attained age as covariates.

Results: In total, 2308 patients answered the questionnaire. Median attained age was 33.5 years (range: 24.9 - 94.5), and median time from treatment was 18.8 years (range: 7.0 - 32.2). Overall, Global health status was good, mean: 75.4, SD: 20.0. Treatments significantly affected QoL in many subscales; CT: dyspnea, financial difficulties, impaired social function, MTOL: impaired global health status, fatigue, dyspnea, financial difficulties, impaired physical function, impaired cognitive function, and impaired social function. Neurotoxicity was closely correlated to treatment; CT was associated with three of four subscales; CT and MTOL were associated with all subscales. When adjusting QoL outcomes for neurotoxicity, all negative associations between QoL and treatment disappeared except dyspnea and impaired social function in the MTOL-group. Neurotoxicity was associated with all EORTC-subscales (p < .001).

Conclusions: Treatment with BEP and MTOL were associated with several QoL subscales in GCCS. However, when adjusting for neurotoxicity the associations generally disappeared. Neurotoxicity correlated strongly with QoL.

Legal entity responsible for the study: Rigshospitalet

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Disclosure: All authors have declared no conflicts of interest.

Large retroperitoneal lymphadenopathy (RPLN) and increased risk of venous thromboembolism (VTE) in patients (pts) with metastatic germ cell tumours (mGCC) a global germ cell cancer group (g3) study

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Background: Prior data indicate that large RPLN significantly increases the risk of VTE in pts with mGCC receiving first line platinum based chemotherapy (chemo). The aim of this multinational G3 study was to validate large RPLN as a risk factor for VTE and evaluate other predictive factors.

Methods: Data were collected retrospectively from sequential pts with mGCC receiving first line chemo from 2000-2014 at 22 centres. Pre-defined variables of interest included IGCCCG risk classification, axial long axis diameter of largest RPLN, Khorana score (validated predictor for chemo associated VTE), LDH, prior VTE and presence of venous access device (VAD). VTE occurring at baseline, during chemo and within 90 days of completion were analysed. Pts receiving thromboprophylaxis (TP) were excluded. Predictive accuracy was assessed using logistic regression and discriminatory accuracy explored using area under the receiver operating curve (AUC).

Results: Data from 1135 pts were collected. Median age was 31 (range 10-74). Testicular primary (92%), non-seminoma histology (72%) and BEP chemo (82%) were most common. IGCCCG risk distribution was 64% good, 20% intermediate and 16% poor. VTE occurred in 150 pts (13%). RPLN >3.5cm demonstrated highest discriminatory accuracy (AUC 0.68, p < 0.001). RPLN >3.5cm was associated with significantly higher risk of VTE (22% versus 8%, OR 3.4, p < 0.001). Univariable analyses identified other risk factors: retroperitoneal primary (OR 5.4, p < 0.002), poor prognosis (OR 3.8, p < 0.001), LDH 5-10xULN (OR 3.9, p < 0.001), prior VTE (OR 3.5, p < 0.001), VAD (OR 3.8, p < 0.001) and Khorana score ≥2 (OR 3.9, p < 0.001). Multivariable analyses confirmed RPLN >3.5cm as an independent risk factor for VTE (OR 2.6, p < 0.001). Other factors maintaining significance include retroperitoneal primary (OR 3.5, p < 0.001), Khorana score ≥3 (OR 2.9, p < 0.001), prior VTE (OR 1.9, p < 0.015) and VAD (OR 2.9, p < 0.001).

Conclusions: This study confirms large RPLN (>3.5cm) as an independent risk factor for VTE in mGCC pts receiving first line chemo. Prospective trials examining TP in this high risk population are warranted.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
Methods: mUC pts previously treated with ≥ 1 prior chemo were enrolled using a modified continual reassessment method design. Strikingly expression was determined by immunohistochemistry (IHC). Disease assessments were performed every 8 weeks (wks) using RECIST v 1.1. ASG-15ME was administered IV weekly for 3 out of every 4 wks until no further benefit. Six dose levels were studied: 0.1, 0.25, 0.5, 0.75, 1, and 1.25 mg/kg.

Results: Of 52/216, 51 pts were enrolled. 93% were SLTRxR positive. Median age was 64 yrs; 100% were ECOG PS ≤ 1; 26 pts (52%) had ≥ 2 prior therapies (tx). Of 42 evaluable pts at doses considered active (doses ≥ 0.5 mg/kg), 1 has a complete response (CR) currently at 39 wks and 13 had a partial response (PR) (ORR = 33%), including 4/11 pts (36%) with liver metastases and 5/12 pts (42%) who failed checkpoint inhibitor (CI) tx. Median duration on ASG-15ME is currently 13 wks. Median progression free survival and duration of response are 16 and 15 wks, respectively. 42 pts (91%) had adverse events (AEs). The most common tx-related AE was fatigue (44%). 23 pts (50%) had Grade (G) 3/4 AEs, 9 (20%) of which were considered related. Ten pts had reversible ocular AEs (1 G3). 4 pts had protocol defined dose limiting toxicities. There were 2 deaths, none related to tx. Serum concentrations of ASG-15ME decreased multi-exponentially and half-life is 3.1 days. Exposure was dose-proportional. Enrollment continues at the 1 and 1.25 mg/kg dose levels to define a dose for future studies. Updated results will be presented.

Table 78OPD Antitumor Activity

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>0.5</th>
<th>0.75</th>
<th>1</th>
<th>1.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficaceous (%: n = 42)</td>
<td>8</td>
<td>14</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>ORR (CR + PR): (%)</td>
<td>1</td>
<td>13</td>
<td>4</td>
<td>27</td>
</tr>
</tbody>
</table>

* ≥ 1 dose of drug and ≥ 1 post-baseline DA

Conclusions: ASG-15ME, a novel ADC, is well tolerated with encouraging antitumor activity in heavily pretreated mUC pts. These results warrant further studies in mUC.

Clinical trial identification: Protocol AGS15E-13-1

Legal entity responsible for the study: Agensys Inc.

Funding: Agensys Inc.

Disclosure: D. Petryyk; Bayer, Bellcosum Pharmaceuticals, Duradoen, Sanofi, Johnson & Johnson, Exelixis, Ferring, Millennium, Medivation, Pfizer, Progenics, Genentech, Alcestis, Oncogenics, Merck, GTX, and Novartis. E. Heath: I do business with or have received research funding from the following companies: Agensys, Bayer, Duradoen, Sanofi, Tokai Pharmaceuticals, Seattle Genetics, Genentech/Roche, and Sanofi E. Gartner; Seattle Coldex, Iovio Pharmaceutical and Celgene. G. Sonopade; Bayer, Genentech Inc, Sanofi, Merck, Novartis, Pfizer, Argos Therapeutics, Agensys Inc. Onxy, Bayer and Boehringer Ingelheim. S. George: I have done business with or have received research funding from the following companies: Genentech, Bayer and Dendreon. J. Picus, B. Anand, K. Morrison, L. Jackson: Agensys Inc. S. Cheng; ROC Roche Boehringer Ingelheim. S.J. Hoffer; Astellas Scientific and Medical Affairs, Janssen Oncology, Janssen Pharmaceuticals, Oncogenex, Astra Zeneca, Novartis, B. Zhong; Astellas, A. Ademi Santiago-Walker, J. Bussolari, F.R. Luo, H. Xie. P. Hammerman: Consultant/Advisory: Janssen. All other authors have declared no conflicts of interest.

Safety and activity of the pan-fibroblast growth factor receptor (FGFR) inhibitor erdafitinib in phase 1 study patients with advanced urothelial carcinoma

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Background: Erdfatinib (INJ-42756493) is a potent, oral pan-FGFR tyrosine kinase inhibitor that demonstrated encouraging preliminary clinical activity and manageable adverse events (AEs) in its first-in-human phase 1 study in advanced solid tumors (NCT01793481). Here we report results from patients with urothelial carcinoma (UC) from this study.

Methods: This 4-part study enrolled patients ages ≥ 18 years with advanced solid tumors. Dose escalation (Part 1) followed a 3 + 3 design, with patients receiving ascending doses of erdafitinib either orally daily (QD) or intermittently (7 days on/7 days off). Subsequent parts of the study (Part 2, pharmacodynamics cohort; Parts 3 and 4, dose-expansion cohorts for recommended phase 2 doses of 9 mg QD and 10 mg intermittently, respectively) required documented FGFR-biomarker positive disease (including activating mutations and translocations, or other FGFR-activating aberrations, Parts 2 and 3).

Results: Twenty-eight patients with UC were treated at 2 mg QD (n = 1), 9 mg QD (n = 13), 10 mg intermittent (n = 13), 12 mg QD (n = 1), or 12 mg intermittent (n = 1). Across these dose levels, median treatment duration was 3.3 mo. The most common drug-related AEs were hyperphosphatemia (57%), dry mouth (50%), diarrhea (46%), and dry skin (46%); all of these were grade 1 or 2 severity, except for 1 case of grade 3 hyperphosphatemia (4%) and 2 cases of grade 3 diarrhea (7%). The most common grade ≥ 3 AEs were anemia (18%), hand-foot syndrome (14%), and stomatitis (11%). Among FGFR-positive, response evaluable patients (as of 22 Apr 2016), the objective response rate (Complete Response + Partial Response (PR)) was 43.3% (10/23; 95% CI 23.2%, 65.5%); 17.4% (4/23) had stable disease. 6/14(42.9%) patients treated at 9 mg QD and 4/11(36.4%) patients treated 10 mg intermittent achieved PR. With a median follow-up of 3.8 mo, median duration of response was 7.2 mo (95% CI 3.3, 13.5) and progression-free survival was 5.1 mo (95% CI 2.8, 5.9).

Conclusions: Erdfatinib is producing encouraging clinical activity and tolerability in patients with FGFR-positive UC, warranting further study.

Legal entity responsible for the study: Janssen Research & Development, LLC

Funding: Janssen Research & Development, LLC

Background: Up to half of mUC pts are ineligible for cis due to ECOG PS or comorbidities. These pts have been underserved in clinical trials and have a high unmet need. Carboplatin-based regimens are associated with notable toxicity, transient responses and mOS of 6–9 mo. Atezo is effective and tolerable in platinum-treated mUC and was tested in cis-ineligible pts as 1L treatment (tx).

Methods: Cis ineligibility criteria included any of: renal impairment (CrCl 30–60 ml/min), hearing loss (≥ 25 dB hearing loss at 2 contiguous frequencies), ≥ ECOG PS2 (Table). Responses occurred across all IC subgroups, in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pts) and PRs occurred in pts with poor prognostic factors and were durable (14, 25) in IC1/2/3 and 16% (12, 20) in all pts. Both CRs (15% in IC2/3; 9% in IC1/2/3; 7% in all pt
Table: 783P Median OS in Nivolumab210° Cohort 2 Subgroups

<table>
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<th>Subgroup</th>
<th>n</th>
<th>95% CI</th>
<th>n</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>All</td>
<td>28</td>
<td>11.9</td>
<td>35.4</td>
<td>35.4</td>
<td>28.9</td>
<td>12.3</td>
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Prior regimen for mUC

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<th>n</th>
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<th>n</th>
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<tr>
<td>≥1</td>
<td>28</td>
<td>11.9</td>
<td>35.4</td>
<td>35.4</td>
<td>28.9</td>
<td>12.3</td>
<td>38.0</td>
</tr>
<tr>
<td>1</td>
<td>24</td>
<td>8.5</td>
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<td>21.2</td>
<td>28.4</td>
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Efﬁcacy outcomes

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<tr>
<td>ORR (conﬁrmed)</td>
<td>25.0 (95% CI)</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>2.8 (1.3–5.0)</td>
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<tr>
<td>Median OS, mo (95% CI)</td>
<td>22.4 (9.7–32.0)</td>
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<tr>
<td>Minimum duration of response, mo (95% CI)</td>
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</table>

Clinical trial identiﬁcation: NCT01928394
Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb


Table: 784P

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<th>Metastatic site</th>
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<th>Nivolumab (N = 78)</th>
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<tr>
<td>Bladder</td>
<td>79.2</td>
<td>22.4 (9.7–32.0)</td>
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<tr>
<td>Liver</td>
<td>79.2</td>
<td>11.9 (3.5–50)</td>
</tr>
<tr>
<td>Liver, lymph node</td>
<td>79.2</td>
<td>79.2</td>
</tr>
<tr>
<td>Lung</td>
<td>79.2</td>
<td>Not estimable (NE)</td>
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</table>

Conclusions: Nivolumab monotherapy in metastatic urothelial cancer (mUC) Updated efﬁcacy by subgroups and safety results from the CheckMate 032 study

Nivolumab monotherapy in metastatic urothelial cancer (mUC): Updated efﬁcacy by subgroups and safety results from the CheckMate 032 study

Background: Nivolumab has shown promising efﬁcacy and acceptable safety in an open-label, multicenter phase I/I study in patients (pts) with mUC after ≥1 prior platinum-based therapy (NCT01928394). Here we report updated efﬁcacy and safety results for the overall population based on additional follow-up and outcomes by differing levels of PD-L1 expression.

Methods: Pts with mUC, unselected by PD-L1 expression status, received nivolumab 3 mg/kg IV every 2 wk until progression or discontinuation. Pts who met protocol criteria could continue treatment beyond progression and cross over to nivolumab + ipilimumab. Tumor PD-L1 membrane expression was assessed with Dako PD-L1 immunohistochemical staining. Primary endpoint: objective response rate (ORR). Other endpoints: safety, progression-free survival (PFS), overall survival (OS), and duration of response.

Results: Of 78 treated pts (median age 65.5 years; range, 31–85), 52 received ≥2 prior therapies. At a minimum follow-up of 9 months, 23.1% of pts on monotherapy and 23.1% switched to combination. Treatment discontinuation was marked by disease progression. PD-L1 was evaluable in 78 pts (86%). Table shows overall efﬁcacy. In pts with PD-L1 expression ≥1% (n = 23) vs <1% (n = 42), ORR was 24% (95% CI: 9.4–45.1) vs 26.2% (13.9–42.0); median PFS, 5.5 mo (95% CI: 1.4–11.2) vs 2.8 mo (1.1–6.5). Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 21.8% of pts; most frequent were fatigue (5.1%), anemia (3.8%) and fatigue, neutrophils, rash, lymphocyte and dyspnea (2.6% each); grade 5 TRAEs occurred in 2.6% (pneumonitis and thrombocytopenia, each). OS by PD-L1 expression and additional subgroup analyses will be presented.

Conclusions: Nivolumab showed encouraging efﬁcacy and acceptable safety regardless of PD-L1 expression in nivolumab previously treated, unselected pts with mUC.
Fibroblast growth factor receptor 3 (FGFR3) mutant muscle invasive bladder cancers (MIBC) are associated with low immune infiltrates

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Background: Activating FGFR3 mutations occur in about 15% MIBC and 70% non-MIBC (NMIBC), raising the potential for FGFR inhibitors as a therapy option. Clinical trials of anti-programmed cell death protein 1 (PD-1) and anti-programmed death ligand 1 (PD-L1) agents have shown benefit in advanced bladder cancer patients and provided evidence for PD-L1 as a predictive marker. We have assessed the association of FGFR3 mutations with FGFR3 expression, PD-L1 and T-cell infiltrates in MIBC samples.

Methods: FGFR3, PD-L1 and CD8 (cytotoxic T-cell marker) expression were assessed by immunohistochemistry (IHC) and FGFR3 mutations by SNaPshot analysis in a cohort of 60 MIBC. FGFR3/PD-L1 expression were also assessed in 40 MIBC, 30 NMIBC and 18 normal urothelium (NU) tissues.

Results: FGFR3 expression (HI-score >20) was observed in 20% (8/40) of MIBC compared to 60% (23/39) of NMIBC while 94% (7/18) were negative. In contrast, FGFR1 expression was high and did not differ between MIBC, NMIBC and NU. FGFR3 mutations were detected in 16% MIBC (10/60) and an association was observed with FGFR3 expression (p < 0.05). In MIBC the prevalence of tumour cell (TC) PD-L1 positivity (defined as ≥25% cells positive) was 12% (7/59) and immune TC positivity was 32% (19/59) and FGFR3 mutant samples all displayed low TC PD-L1 (<25% expressing PD-L1) and low CD8 (<25cells/mm² positive) expression. For FGFR3 wild-type tumours, PD-L1 TC positivity ranged from 0–70% cells (26% cancers with >5% cells PD-L1 positive) and CD8 from 5–143 cells/mm² (23% with >250 cells/mm² positive). Consistent with these observations, the Cancer Genome Atlas MIBC data set showed FGFR3 mutant/fusion bladder cancers cluster into a low immune subtype.

Conclusions: FGFR3 mutation is associated with increased FGFR3 expression and low PD-L1 and cytotoxic T-cell infiltrates, suggesting these tumours may respond differently to anti-PD1/PD-L1 therapy and supporting investigation of FGFR3 inhibitors as a therapeutic option. Clinical studies with FGFR inhibitors in bladder cancer are ongoing, including assessment of AZD4547 in monotherapy and combination with anti-PD1/PD-L1 agent durvalumab (NCT02546661).

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Disclosure: E. Kilgour, H. Angel, N.R. Smith, M. Ahmedskii, J.C. Barrett, E.A. Harrington Employee of AstraZeneca and holds stock in AstraZeneca. All other authors have declared no conflicts of interest.

Interim analysis of a phase I dose escalation trial of ASG-22CE (ASG-22ME; enfortumab vedotin), an antibody drug conjugate (ADC), in patients (Pts) with metastatic urachal tumor (mUC)

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Background: Nectin-4 is a protein expressed on several tumors, including mUC. Enfortumab vedotin is an ADC that delivers a small molecule microtubule-disrupting agent, monomethyl auristatin E (MMAE), to tumors expressing Nectin-4. In a phase II study of cabozantinib in patients (pts) with relapsed/refractory metastatic urachal urethelial carcinoma (mUC)

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Background: Hepatocyte growth factor (HGF) and its receptor (MET) are activated in UC. In translational studies, cabozantinib, a receptor tyrosine kinase inhibitor primarily targeting MET and VEGFR2, reversed HGF-driven UC cell growth and invasion.

Methods: In this phase II study, pts received cabozantinib 60 mg/day in 28-day cycles in 3 cohorts: 1) mUC, 2) bone-only mUC, and 3) metastatic rare bladder histology. Primary objective was overall response rate (ORR) by RECIST v1.1. In cohort 1, we also report on the tumor responses by site of metastases (mets). Secondary objectives were to assess the progression-free survival (PFS) and overall survival (OS) in all cohorts.

Results: Of 67 pts enrolled, 70% of male, average age: 63 (22–82), KPS 80% in 73% pts. Primary sites: 69% bladder, 25% upper tract, 6% both. No. prior therapies: 1/2/3/4 (range 1–6) in 34/39/16/9% of pts, respectively. Of 41 evaluable pts in cohort 1, there was 1 complete response (CR), 7 partial responses (PR) (ORR ≥ 19.5%, 95% CI: 8.8–34.9), 18 stable disease (SD), and 15 progressive disease (PD). Median progression-free survival (mPFS): 3.7 mos (95% CI: 2.3–6.3); median PFS: 38.0% (95% CI: 23.3–52.6%). Median overall survival (mOS): 8.2 mos (95% CI: 5.2–10.3); 6-month OS: 65.1% (95% CI: 48.3–77.6%); 12-month OS: 25.7% (95% CI: 13.0–40.3%). ORR in cohort 1 was evaluated by site of mets in 63 target-lesions: 25.3%non/9.5%alive/6.3%adrenal/1.6%/kidney/1.6%pancreatic/38.4%/LN/15.9% ST. Lung mets had 25% PR/75% SD/PD. Treatment resulted in lung lesion cavitation, which could not be interpreted as CR (at best PR). Liver mets had 83.3%/16.7%/PD. There was no ORR in liver/ adrenal/kidney/pancreatic mets. LN mets had 8% CR/8%PR/72%SD/12%PD. ST mets had 90%SD/10%PD. Of 5 pts in cohort 2, 60% had improvement by NaF PET/CT. mOS: 9.3 mos (95% CI: 3.6–12.5). Of 10 evaluable pts in cohort 3, there were 9PR/ CR/15SD/2PD. mPFS: 2.9 mos (95% CI: 1.8–3.7); mOS: 4.6 mos (95% CI: 2.6–8.0).

Conclusions: Cabozantinib has clinical activity in relapsed/refractory pts with mUC. Lung and LN mets had higher ORR. Lung lesion cavitation was frequently noted in responders. Further studies are underway to correlate responses with MET expression, immune subsets, CTCs, and cytotoxic/mutational profiles.

Legal entity responsible for the study: NC1/NIH

Funding: CTEP NIH

Disclosure: All authors have declared no conflicts of interest.
Results: As of 4/29/16, 49 solid tumor pts were enrolled. 42 with mUC reported here. Of analyzed tumor tissues, 98% were Nectin-4 positive (93% had H-score ≥150). Median age 67 y; 100% EGCG PS ≤1, 25 mUC pts (60%) had ≥2 prior therapies (tx). Of 35 response evaluable pts, 10 had a partial response (PR) (ORR =30%), including 4/10 pts (40%) with liver metastasis and 31/32 (25%) who had adverse events (AEs). The most common tx related AE was fatigue (38%). 23 pts (55%) had Grade (G) 3/4 AEs, 10 pts (24%) considered related. 9 pts (21%) had omar ACs (G1/G2). 2 pts had protocol defined dose limiting toxicities. There were 2 deaths, unrelated to tx. Serum concentration of enfortumab vedotin decreased with a multi-exponentially half-life of 1.6 wks. Exposure was dose proportional. Expansion cohorts are open at 1.25 mg/kg; updated results will be presented.

Table: Table 788P. mUC pts Only

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>N</th>
<th>Cmax, ng/mL</th>
<th>AUC0-24h, ng*h/mL</th>
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<td>0.5</td>
<td>1</td>
<td>1,140 (44.8)</td>
<td>21,900 (44.8)</td>
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<tr>
<td>0.75</td>
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<td>34,000 (50.2)</td>
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<td>1.6</td>
<td>1</td>
<td>2,160 (60.2)</td>
<td>31,900 (115.7)</td>
</tr>
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</table>

* Approximately 3% of total mUC is unbound in plasma.

Conclusions: Exposure for the pan FGFR inhibitor erdafitinib at 9 mg C, 10 mg I, and 12 mg I achieved or exceeded the targeted therapeutic range in patients with urothelial carcinoma and FGFR aberrations. Concurrent use of a phosphate binder did not affect erdafitinib PK.

Clinical trial identification: NCT01703481

Funding: Janssen Research & Development, LLC

Legal entity responsible for the study: Janssen Research & Development, LLC

Background: Despite platinum-based chemotherapy nearly 40% of patients (pts) with localized muscle-invasive urothelial carcinoma (mUC) will develop recurrent disease following surgical resection. The aim of this analysis was to identify whether differentially expressed protein biomarkers in tumor tissue may predict disease recurrence.

Methods: Tissue samples were obtained from 57 pts who underwent curative surgical resection at “University Hospital 12 October” between 2006 and 2012. Medical records were reviewed for histology, stage, adjuvant chemotherapy, disease-free survival, and overall survival. We have analyzed the proteome applying a high-throughput proteomics approach to routinely archived formalin-fixed, paraffin-embedded tumor (FFPE) tissue. Protein extracts from FFPE samples were prepared in 2% SDS buffer and digested with trypsin. SDS was removed from digested lysates, and resulting peptides were analyzed in a Q-Exactive high mass spectrometer.

Protein abundance was calculated on the basis of the normalized spectral protein intensity (LFQ intensity) using MaxQuant. A prognostic protein signature was built.

Results: 57 pts with a median age of 65.9 years were included in the analysis. After a median follow up of 38 months, 26 (45%) pts relapsed. We were able to identify and quantify 1,456 proteins. Supervised analyses identified 6 proteins associated with higher risk of relapse (5 year DFS 70% vs. < p = 0.001), HR 3.53, [95% CI 1.8 – 6.7]). By stage status at time of surgery the protein profile remained significant: stage III (5 year DFS 67% vs. 20%, p = 0.001) and stage IV (5 year DFS 70% vs 20%, p = 0.001).

Conclusions: The discovery of proteins as biomarkers in bladder cancer is feasible. In this preliminary analysis we identified 6 proteins that can predict the outcome of surgery.
patients with MUC4 as prognostic factor. Additional validation analysis will be performed. Supported by a grant from the FMM (2012-0085).

Legal entity responsible for the study: N/A

Funding: FMM (Fondazione Mutua Madrèlina)

Disclosure: G. De Velasco: Advisory Board: Pfizer. No conflicts with the abstract presented.

All other authors have declared no conflicts of interest.

Transcriptomic analysis of collecting duct carcinoma of the kidney

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Background: Collecting duct carcinoma (CDC) of the kidney is a rare tumor. It originates from the renal medulla, and it represents less than 2% of all renal tumors. The clinical course of this disease is characterized by aggressive behavior. The locally advanced and/or metastatic presentation, along with the resistance to treatments, confer CDC an unfavourable prognosis. Due to its rarity, little is known about CDC biology, and to date no targeted therapy is available. Here, we aimed to identify deregulated pathways that discriminate between CDC, clear cell carcinoma (CCC) and healthy renal tissue.

Methods: We collected 9 cases of CDC treated at Istituto Nazionale dei Tumori (Milan), together with 7 cases of CCC and 7 healthy normal adjacent renal tissues (NAT). Gene expression profiling was performed by GeneChip® Human Transcriptome Array 2.0 (HTA 2.0 – Affymetrix). 827 coding and 52 non-coding genes were differentially expressed between the three subtypes (p < 0.05).

Results: Among those genes, we confirmed the differential expression levels of fibronectin 1 (FN1), periostin (POSTN) and stratifin (SFN), by Real Time PCR. The subsequent functional enrichment analyses identified histone modifications, cytoplasmic ribosomal proteins, senescence, autophagy and focal adhesion pathways as the most deregulated in CDC vs both CCC and normal tissues.

Conclusions: Our analysis, in agreement with clinical observations, suggests that CDC genetic basis should be considered distinct from other renal tumors. A better understanding of the specific molecular alterations causally involved in this disease may lead to new prognostic factors and therapeutic approaches for this currently incurable malignancy.

Legal entity responsible for the study: N/A

Funding: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy Ohio State University Medical Center, Columbus, Ohio, USA Pelotonia, The Ohio State University, Columbus, Ohio, USA

Disclosure: All authors have declared no conflicts of interest.

Clinical significance of early circulating tumor cells (CTC) changes, analyzed by AdnaTest, in patients (pts) receiving first-line methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy (CT) for metastatic urothelial cancer (UC)

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Background: The therapeutic paradigm of metastatic UC is rapidly shifting due to the availability of targeted agents. UC receiving MVAC CT. Early CTC changes may be useful to improve our prognostic ability. Pending validation, these results may lead to improved trial designs and to refine the sequence of conventional CT options in the clinical setting.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori

Funding: Fondazione IRCCS Istituto Nazionale dei Tumori

Disclosure: All authors have declared no conflicts of interest.

Impact of race on survival following radical cystectomy for muscle-invasive bladder cancer (MIBC): Analysis of the US National Cancer Database (NCDB)

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Background: The impact of race as an independent factor on overall survival (OS) following radical cystectomy (BC) for muscle invasive bladder cancer (MIBC) is unclear. Small retrospective studies suggest an unfavorable impact of black race on outcomes. We conducted a retrospective analysis of the large NCDB database to

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evaluate the impact of race, specifically African American race, in patients undergoing RC for MIBC.

Methods: The NCDB was employed including patients (pts) with new diagnoses of urothelial carcinoma of bladder who underwent RC in the US from 2004-2013. Those with prior malignancy and prior radiotherapy were excluded. Race status was collected as white (W), black (B), white Hispanic (H) and Asian or Pacific Islander (API). Multivariate analyses were conducted to determine whether race conferred an independent impact on OS in 3 separate cohorts: those who underwent RC alone, those who underwent neoadjuvant chemotherapy (NC) and those who underwent adjuvant chemotherapy (AC) after controlling for baseline stage (clinical stage for NC group, and pathologic stage for RC and NC groups), age, year of diagnosis, Charlson Comorbidity Index (CCI), number of lymph nodes examined at RC and gender.

Results: A total of 31,619 pts were available for analysis: 18,939 in the RC group (W = 17,117, B = 1075, H = 481, API = 266), 4059 in the AC group (W = 3672, B = 236, H = 107, API = 44) and 621 in the NC group (W = 744, B = 443, H = 204, API = 124). On multivariate analysis, black race was statistically significantly and independently associated with poor OS compared to white race in the RC alone (HR = 1.17, p = 0.0004), AC (HR = 1.32, p = 0.0007) and NC (HR = 1.21, p = 0.0034) groups. Limitations of a retrospective analysis apply.

Conclusions: Black race was validated to be an independently significant poor prognostic factor for OS in this large cohort of pts with bladder cancer undergoing RC with or without perioperative chemotherapy. The incorporation of race in post-operative nomograms and prognostic models is warranted to improve risk stratification.

Legal entity responsible for the study: City of Hope

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Randomized placebo controlled phase II trial (MAJA): Efficacy results of maintenance vinflunine after cisplatin chemotherapy (CT) in patients with advanced urothelial carcinoma (UC), SOGUG 2011-02


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Background: Vinflunine (VFL) is a microtubule inhibitor approved by EMA as treatment after platinum progression in metastatic UC. We evaluated whether maintenance VFL delays progression after response to CT.

Methods: Patients (pts) with measurable disease, locally recurrent/metastatic UC and adequate organ function with radiological response or stabilization after 4 cycles (cy) of a cisplatin/gemcitabine chemotherapy (carboplatinallowed after cy 4) were randomized (R) 1:1 to receive VFL 320 or 280mg/m2 (in case of PS1, age 75years, α-error of 0.05(one-tailed test) and a 0.1β-error of 0.05) in VFL arm and 60% of pts at BSC arm. The median PFS was of 6.5m(1.3-11.7) in the VFL arm and 4.6m (3.1-6) in the BSC arm. The median PFS was of 6.5m(1.3-11.7) in the VFL arm and 4.6m (3.1-6) in the BSC arm. The median PFS was of 6.5m(1.3-11.7) in the VFL arm and 4.6m (3.1-6) in the BSC arm.

Results: 88pts from 21 institutions of SOGUG were R between 04/2012-01/2015. Forty five in the VFL arm and 43 unthe BSC arm. 1pt was not treated. 1 of 87 treated pts was not due to an excess of time between the last dosef cisplatin and the start of VFL. At the beginning of treatment median age 64years (42-83), PSI 50%, Hb <10g/dl 8% liver metastasis 21%. Pts in the VFL arm received a median of 6 cycles per patient [1-41). 10pts (22.2%) continue treatment in VFL arm. Most common G3/4AEs (9pts) in VFL arm were constipation (13.6), neutropenia (15.9), fatigue(15.9), and 16hr ileus (11.3). After a median of 12.2m of follow-up [0.5-41.4], 59% of pts have progressed (43% of pts have died in the VFL arm, 81% and 62% pts respectively in the BSC arm. The median PFS was of 6.5m(1.3-11.7) in the VFL arm and 4.6m (3.1-6) in the BSC arm. HR 0.56 (IC95%; 0.34-0.93, p = 0.024). After progression, 34%of pts received treatment at VFL arm and 60% of pts at BSC arm.

Conclusions: Maintenance VFL significantly reduced the risk of disease progression in patients with metastatic disease obtaining benefit from first line cisplatin-based CT. Treatment was well tolerated. Data is maturing to assessits impact in overall survival.

Clinical trial identification: EudraCT 2011-00127-39

Legal entity responsible for the study: SOGUG - Spanish Oncology Genito/Urinary Group

Funding: SOGUG - Spanish Oncology Genito/Urinary Group

Disclosure: All authors have declared no conflicts of interest.
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Background: The available prognostic models of OS for pts with metastatic UC were derived from clinical trial populations of cisplatin-treated pts only. We aimed to develop a new model based on real world pts.

Methods: Individual pt-level data from 29 centers was collected. Pts had to be treated for metastatic UC at the participating sites between 01/2016 and 01/2011. Selection criteria included metastatic UC, and first-line cisplatin- or carboplatin-based chemotherapy. The overall sample was randomly split into a development and a validation cohort. Variables were selected using the backward variable selection, and the second incorporating objective response (OR). The performance of the present nomogram and that of the other available models was assessed for accuracy (Brier score), calibration (Hosmer-Lemeshow test), and discrimination (Harrell c-index).

Results: Of 1974 mUC patients 475 (25%) did not receive 1st-line chemotherapy. No significant proportion of patients do not receive chemotherapy, while about 50% of treated patients do not receive cisplatin. We used the multinational RISC database to map patterns of chemotherapy utilization and adherence to recently published UFC criteria (Galicky, 2011) in unselected mUC patients

Methods: Selection criteria: diagnosis of mUC, transitional-cell, mixed, squamous and adeno histologies.

Results: Of 1974 mUC patients 475 (25%) did not receive 1st-line chemotherapy. No significant proportion of patients do not receive chemotherapy, while about 50% of treated patients do not receive cisplatin. We used the multinational RISC database to map patterns of chemotherapy utilization and adherence to recently published UFC criteria (Galicky, 2011) in unselected mUC patients

Conclusion: Nomogram-based prediction of overall survival (OS) of patients (pts) with metastatic urothelial carcinoma (UC) receiving first-line platinum-based chemotherapy: retrospective international study of invasive/advanced cancer of the urothelium (RISC)
Background: Adherence to cisplatin-based regimens prescription in “fit” patients fulfilling platinum eligibility criteria. Impact on outcomes: a retrospective international study of invasive/advanced cancer of the urothelium (RISC) analysis

Method: Selection criteria: diagnosis of uM, transitional, mixed, squamous and adenocystic, survival data available. Major end point: Overall survival (OS). Cisplatin was defined according to Galsky et al (2011).

Results: From 1828 uM patients 441 (24%) did not receive any chemotherapy. These patients had a significantly shorter median OS (Table). 1361 patients (median follow-up: 31 months) were included in the analysis of the following treatment types: cisplatin-based chemotherapy (n = 689), carboplatin-based (n = 404), no cis- or carbo-platin (n = 268) on patients fulfilling platinum eligibility criteria. Impact on outcomes within the FOCP.

Conclusion: The results are consistent with real-life data from Europe (Spanish, German and French) presented at ESMO 2013. Toxicity has been further reduced with the use of prophylactic laxative treatment, which is consistent with real-life data from Europe (Spanish, German and French) presented at ESMO 2013.

Legal entity responsible for the study: University of Liverpool

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 799P

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<th>1st-line chemotherapy</th>
<th>Median OS (months)</th>
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<td>Yes (n = 1499) No (n = 475)</td>
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<td>13.4-15.5</td>
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<td>Treatment Group Cisplatin (n = 689) Carboplatin (n = 404)</td>
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<td>14.8-18.5</td>
<td>&lt;0.001</td>
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<td>Ufit-for-cisplatin Yes (n = 550) No (n = 421)</td>
<td>15.8 (IQR: 9.8)</td>
<td>14.1-18.7</td>
<td>&lt;0.001</td>
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<td>Cisplatin-treated Fit-for-cisplatin (n = 295) Ufit-for-cisplatin (n = 182)</td>
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<td>14.9-24.2</td>
<td>&lt;0.001</td>
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<td>Cisplatin-treated Fit-for-cisplatin (n = 120) Non-cisplatin treated Ufit-for-cisplatin (n = 368)</td>
<td>9.4 (IQR: 1)</td>
<td>9.4-14.7</td>
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demonstrated modest activity. The treatment and outcomes of real-world patients with mUC treated with second-line (2L) systemic therapies remains underexplored.

Methods: Pts diagnosed with stage IV transitional cell carcinoma of the bladder from 1/2004 to 12/2011 were identified in the US SEER-Medicare database. Other criteria included 2 or more positive biopsies at diagnosis (1 y after previous diagnosis and carcinoma diagnosis in Medicare Parts A and B). 2L chemotherapy regimens were defined as any change in 1L chemotherapy or start of new treatment upon completion of 1L. Kaplan-Meier methods were used to assess survival by 2L treatment approach (follow up through 12/2013).

Results: 240 mUC pts treated with 2L chemotherapy were included. Median age at diagnosis was 73 y (IQR 71-79 y), and 81% of pts were aged ≥ 70 y. 74% were male and 93% were white. Most pts (99/240, 41%) received cisplatin- or carboplatin-based prior 1L therapies. The most common comorbidities included diabetes (16%) and chronic obstructive pulmonary disease (10%). Among pts receiving 2L chemotherapy, 40% (97/240) received single agents. The majority of pts who received single agents had taxanes (paclitaxel 78/97, 38%, docetaxel 20/97, 21%), followed by gemcitabine (19/97, 20%) and other single agents (21/97, 21%). The median overall survival (OS) in pts receiving any single-agent 2L chemotherapy was 6.4 mo (95% CI 4.4–8.5 mo) with a 24-mo OS rate of 13%. The median OS in pts receiving single-agent taxanes was 5.2 mo (95% CI 3.5–8.6 mo), with a 24-mo OS rate of 8%.

Conclusions: In this real-world mUC population, pts received a wide variety of therapies in the 2L setting. Regardless of the treatment approach, outcomes were generally poor with a low likelihood of durable disease control. These results may serve as a benchmark for the effectiveness of novel therapies currently being developed for the treatment of mUC.

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche Ltd.


281 small cell bladder cancer analysis from Spanish institutions


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Background: Some patients with RCC are unsuitable for nephrectomy. SIRT is used for unresectable liver cancers, and has properties that make it potentially useful for primary RCC. RESIRT is the first-in-human study to evaluate safety and feasibility of SIRT for primary RCC.

Methods: Pts not amenable for or who declined conventional therapy were eligible. Metastases were permitted. A single transperitoneal microcatheter administration of yttrium-90 resin microspheres (SIR-Spheres; Sirtex, Australia) was delivered superselectively via the renal artery to the target organ at intended radiation doses of 75, 100, 150, 200, 300 Gy and a final cohort with a procedural endpoint of imminent stasis, in a dose-escalation design. Post-SIRT follow-up was 12 months. The primary endpoint was safety and toxicity at 30 days post-SIRT. Secondary endpoints included tumour response (RECIST v1.1) at 12 months.

Results: The study enrolled 21 pts with RCC, mean age 74.9 years and WHO performance status of 0 (81%) or 1 (19%). Six (29%) pts had metastatic RCC, 7 (33%) had previously undergone total nephrectomy of the contralateral kidney, 1 (5%) received prior chemotherapy, 1 (5%) progressed after cryotherapy to the target organ and 3 (14%) received other prior therapy. Median follow-up is 11.9 months (95% CI 11.8–12.0). The intended doses were delivered without any dose-limiting toxicity. 13/21 (71%) pts experienced 44 AEIs within 30 days post-SIRT. Eight (38%) pts had AEIs grade ≥3; all were unrelated to SIRT. 8 pts (38%) had 12 AEs that were related to SIRT (all grade 1–2, no SAEs), of which 1 occurred pre SIRT. Treatment-related AEs were fatigue/tiredness, pain, hypertension, lack of appetite, ‘heaviness’, bruised gun and hypogammaglobulinaemia. 15 SAEs were reported in 8 (38%) pts; 2 within 30 days post-SIRT (shortness of breath, prolonged hospitalisation). Best overall tumour responses were partial response 1/19 (5.3%), stable disease 17/19 (89.5%) and progressive disease 1/19 (5.3%).

Conclusions: This pilot study demonstrates good tolerability of SIRT at all dose levels including imminent stasis in treating primary tumours in RCC pts otherwise unsuitable for conventional therapy.

Clinical trial identification: Australian New Zealand Trials Registry: Trial ID ACTRN12610000690055

Legal entity responsible for the study: Sirtex Technology Pty Ltd. Funding: Sirtex Medical Limited.


A phase 1b dose-escalation study of TCR105 (endogin antibody) in combination with axitinib in patients with metastatic renal cell carcinoma (mRCC)


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Background: Resistance to VEGF-targeted therapy is a major challenge in contemporary treatment of mRCC, and endogin (CD105) activation may be an important mechanism leading to resistance. Endogin is an extracellular receptor expressed on proliferating tumor vessels and mRCC cancer stem cells, and is upregulated following VEGF inhibition. TCR105 is an endogin monoclonal antibody that potentiates the anti-tumor activity of bevacizumab and VEGF receptor tyrosine kinase inhibitors in preclinical models.

Conclusions: We present the largest published series on SCBC. Outcome data from 281 SCBC cases has not shown statistically significant differences in OS among patients who have undergone RC alone compared to those receiving NeorQQT or AdjQQT (p = 0.75). Furthermore, no significant differences among the different QT schemes were observed.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
Methods: Heavily pretreated mRCC pts with ECOG PS 0-1 and acceptable organ function were treated with TRC105 weekly (8mg/kg and then 10mg/kg) in combination with axitinib (initially at 5 mg BID and then escalated per patient to a maximum of 15 mg BID).

Results: Eighteen mRCC pts (median age = 61.5, M:F=16:2, median number of prior therapies = 3, including >1 VEGFR TKI, clear cell=13, prior axitinib =1) were treated. TRC105 dose escalation proceeded from 8 mg/kg (n=3) to 10 mg/kg (n=15) without dose limiting toxicity. Adverse events characteristic of each drug were not increased in frequency or severity when the two drugs were administered concurrently, and most commonly included epistaxis, headache, fatigue, diarrhea, and gingival bleeding. TRC105 and axitinib demonstrated preliminary evidence of activity, including partial responses in 29% of patients by RECIST 1.1, and longer PFS than expected with axitinib as a single agent. The overall disease control rate (CR/PD/SD > 2 months) was 88% (15 of 17). Median PFS overall was 8.4 months, and was 9.6 months among patients with clear cell RCC. Tumor response will be correlated with baseline protein biomarkers. TRC105 pharmacokinetic parameters will be reported.

Conclusions: TRC105 at 8 and 10 mg/kg was well tolerated in combination with axitinib, with encouraging evidence of activity in patients with mRCC. A multicenter randomized Phase 2 trial of axitinib +/− TRC105 is actively enrolling at this time (NCT01890604).

Clinical trial identification: Protocol # 105RC101 (NCT01890604)

Legal entity responsible for the study: Sponsor: TRACON Pharmaceuticals, Inc. Lead PI: Tony Choueiri

Funding: Sponsor: TRACON Pharmaceuticals, Inc.

Disclosure: T. Choueiri: Consulting or Advisory Role: Pfizer, GSK, Bayer, Novartis Research Funding (institution); Pfizer. M.D. Michaelson: Consulting or Advisory Role: Melleunen, Astellas, Novartis, Medivation Research Funding (institution); Pfizer. Eiss, Argo, Melleunen, Novartis, Tracon. E. Posadas: Consulting or Advisory Role: Medivation, Bavarian Nordic Immunotherapeutics Research Funding (Institution). Janssen, Bavarian Nordic Immunotherapeutics, Tracon. D. McDermott: Consulting or Advisory Role: Genentech, Merck, BMS, Pfizer Research Funding: Prometheus Labs. R. Seon: Grants - Roswell Park Cancer Institute. M. Ijani: Employee of TRACON Pharmaceuticals, Inc. Stock ownership of BMS R. Adams, C. Theuer: Employee of TRACON Pharmaceuticals, Inc. Stock ownership of TRACON Pharmaceuticals, Inc. All other authors have declared no conflicts of interest.

BO8P New insights on oncogenic alterations in clear-cell renal cell carcinoma with sarcomatoid dedifferentiation

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Background: Sarcomatoid dedifferentiation in renal cell carcinoma (sRCC) has been associated with aggressive disease and poor outcome. However, the molecular landscape of sRCC remains largely unknown, especially regarding chromatin remodeling gene alterations and the alterations of wild-type VHL tumors.

Methods: Sixteen primary sRCCs and matched normal tissues underwent whole-exome sequencing, with a median coverage of 110x and 10x for cancer and normal samples, respectively. These data were compared to 417 non-sARCCs from the Cancer Genome Atlas (Cancer Genome Atlas (Cancer Genome Atlas) database. Associations with clinical and pathological tumor features were performed.

Results: Most frequent somatic mutations included VHL (11/16, 69%), and chromatin remodeling genes including PBRM1 (7/16, 44%) and SETD2 (3/16, 19%). BAP1 mutations were only present in 2 cases (12%). These alterations of chromatin remodeling gene mutations were not enriched compared to the TCGA cohort of clear-cell RCC. Of note, chromatin remodeling gene alterations were not mutually exclusive, with concurrent mutations of PBRM1 and BAP1, and PBRM1 and KDM5C reported in one and two patients, respectively. No recurrent alterations of known oncogenic pathways such as MAPK, PI3KCA/mTOR, p53 or tumor mutation were reported. Out of 5 patients (31%) without VHL alterations, 2 (40%) had a metastatic evolution compared to only 18% in patients with VHL mutations. All had at least one alteration of chromatin remodeling genes including BAP1, PBRM1, and SMARCA4. Interestingly, mutational load was not correlated with clinical and pathological tumor features such as Fullman grade and TNM stage, nor with alterations of known oncogenes.

Conclusions: The genetic landscape of sRCC of clear-cell type might not be different from other clear-cell RCC. Patients with wild-type VHL tumors represent nearly one third of those cancers, had more aggressive tumors and constant chromatin remodeling gene alterations. These data underline the urgent need for the characterization of epigenetic modifications that might further explain the distinctive features of sRCC.

Legal entity responsible for the study: Assistance Publique - Hôpitaux de Paris - Groupe Hospitalier Pitié Salpetrière

Funding: Fondation AVEC

Disclosure: All authors have declared no conflicts of interest.
Results: Eleven of 34 evaluable patients (32%) had % tumor reduction >30% with a median of 13.5%. Major adverse events (Grade 3) were hypertension in 17 (43%), proteinuria in 7 (18%), respectively. Among several PK parameters, total clearance (CL-tot; dosage/AUC) was the most significantly associated with patient outcomes, i.e., reverse correlation with % reduction (p = 0.0053; sensitivity, specificity: 76.5%) and proteinuria (p = 0.0357). Surprisingly, hypertension was associate with neither % tumor reduction, nor CL-tot.

Conclusions: Estimated CL-tot may be more beneficial than hypertensive to determine the optimal initial dose of axitinib in individual RCC patient.

Clinical trial identification: UMIN000011147 (2013/07/10)

Legal entity responsible for the study: Institutional Review Board Yamaguchi University Hospital

Funding: Yamaguchi University Hospital Yamaguchi Prefecture

Disclosure: All authors have declared no conflicts of interest.

[Table 810P]

Inverse association between baseline renal function and overall survival in patients with metastatic renal cell carcinoma who were treated with molecular-targeted agents

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Background: Renal toxicity is regarded as one of the most frequently observed adverse events in metastatic renal cell carcinoma (mRCC) patients, irrespective of the type of targeted agent introduced. The objective of this study was to investigate the prognostic significance of the baseline renal function in mRCC patients treated with molecular-targeted agents.

Methods: This study included a total of 408 consecutive mRCC patients receiving molecular-targeted therapy, consisting of 124 (group A) and 284 (group B) who had baseline estimated glomerular filtration rates ≥60 ml/min/1.73 m² and < 60 ml/min/1.73 m², respectively.

Results: Compared with group A, group B was significantly less likely to have poor prognostic factors, such as a high proportion of patients without nephrectomy, unfavorable risk classified by the Memorial Sloan Kettering Cancer Center or Heng’s system, high C-reactive protein level, and high incidence of lymph node, bone or liver metastasis. The median overall survivals (OSs) after the initiation of targeted therapy in groups A and B were 21.4 and 35.8 months, respectively, and there was a significant difference in the OS between these two groups, however, multivariate analysis showed the lack of independent impact of the baseline renal function on the OS. Furthermore, when patients without nephrectomy were excluded, no significant difference was noted in the OS between the two groups.

Conclusions: There appeared to be an inverse association between the baseline renal function and OS in mRCC patients receiving molecular-targeted therapy, suggesting no adverse impact of an unfavorable baseline renal function on the efficacy of targeted agents against mRCC. Accordingly, molecular-targeted therapy should not be avoided in mRCC patients with an impaired baseline renal function.

Legal entity responsible for the study: N/A

Funding: Kobe University

Disclosure: All authors have declared no conflicts of interest.

[Table 811P]

Prognostic ability of early tumor shrinking on overall survival (OS) in metastatic renal cell carcinoma (mRCC) – a validation study

G.R. Pond, J. Dielich, V. Grünwald

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Background: Early tumor shrinking (%TS) of 10% has been identified as a putative prognostic marker in mRCC, which could serve as an early read-out in clinical trials. We aimed to validate the prognostic role of %TS in first-line TKI treatment using data from the COMPARZ study (NCT00720941).

Methods: A retrospective analysis on data of 1100 1st line patients treated with sunitinib or pazopanib was performed. Tumor response was measured according to RECIST 1.1. eTS was a priori defined as tumor shrinkage by 10%.

Results: 1262 mRCC pts initiated 1L therapy between 2011 and 2013 and met selection criteria. Median age was 62 y; 70% were male; 84% had a CCI of 0-1, with diabetes (26%) and chronic kidney disease (19%) being the most frequent. VEGF-directed therapy was more common than mTOR-directed therapy (87% vs 13%). PO therapy was more common than IV therapy (R2 = 0.2542; 83% vs 17%). Diabetes was more common in pts taking VEGF-directed therapy, while the opposite was seen for CHF; these factors remained independently associated with 1L therapy in multivariate analyses (Table). Pts receiving IV therapy were older than those receiving PO therapy (mean, 65 vs 62 y), and age remained significant in the multivariate-adjusted model (P = .04).

Conclusions: Baseline diabetes and CHF as well as age are independent predictors of 1L mRCC treatment selection. Differences in treatment safety profiles and pt health may drive this difference. These results will inform ongoing studies that compare treatment selection in 1L mRCC.

Legal entity responsible for the study: F. Hoffmann-La Roche

Funding: F. Hoffmann-La Roche


[Table 811P]

Prognostic ability of early tumor shrinking on overall survival (OS) in metastatic renal cell carcinoma (mRCC) - a validation study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>Diode Mohan (CI95%)</th>
<th>1-year Survival</th>
<th>OS (CI95%)</th>
<th>2-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1262</td>
<td>329</td>
<td>125 (18.0 - 13.4)</td>
<td>59.9 (53.4, 66.8)</td>
<td>56.8 (51.6, 62.5)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, employment status, geographic region, insurance type, CCI score, and other baseline comorbidities that were statistically significant (P < .05) in univariate analyses.

Conclusions: Baseline diabetes and CHF as well as age are independent predictors of 1L mRCC treatment selection. Differences in treatment safety profiles and patient health may drive this difference. These results will inform ongoing studies that compare treatment selection in 1L mRCC.

Legal entity responsible for the study: F. Hoffmann-La Roche

Funding: F. Hoffmann-La Roche

At 42 and 90, 582 and 1007 patients were evaluable for landmark analysis, of whom 56.5% and 65.2% achieved eTS, respectively. In patients with eTS median OS was 34.1 (95% CI: 29.8-64.1) months, and 33.6 (95% CI: 30.1-64.1) months, respectively. Comparing to the first post-baseline radiological assessment under treatment with a second-line agent and ETS induced by a second-line agent on overall survival (OS) in mRCC patients. The objective of this study was to evaluate the impact of ETS on OS and PFS in 2nd line patients without eTS. There was no interaction between type of treatment and eTS (OR 0.79, 95% CI 0.60-0.90, P<0.05). In multivariable analyses, adjusted for age, sex, performance status, nephrectomy, anemia, neutrophils, platelets, LDH, organs involved, liver metastases, time from diagnosis, calcium, treatment, and baseline tumor burden, eTS ≥10% remained an independent prognostic marker of OS for both 42: HR 0.53 (0.41; 0.69), p < 0.001 and 90: HR 0.49 (0.39; 0.68), p < 0.001.

Conclusions: Similar results were found for eTS at the 42 and 90 days landmarks. eTS ≥10% has prognostic relevance in mRCC and reflects a valid early endpoint in clinical trials.

Clinical trial identification: NCT00720941
Legal entity responsible for the study: GSK sponsored study. Current analysis is retrospective on the available data set.
Funding: Medical School Hannover, McMaster University
Disclosure: V. Grünwald: Honoraria: Novartis, Pfizer, BMS Consultation: Novartis, Pfizer, BMS. All other authors have declared no conflicts of interest.

813P Prognostic significance of early tumor shrinkage under second-line targeted therapy for metastatic renal cell carcinoma: a retrospective multinational study in Japan

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Background: The prognostic significance of early tumor shrinkage (ETS) under second-line targeted therapy for metastatic renal cell carcinoma (mRCC) has not been fully documented. The objective of this study was to evaluate the impact of ETS induced by a second-line targeted agent on overall survival (OS) in mRCC patients.

Methods: This study retrospectively included 271 consecutive Japanese patients with mRCC, who received second-line targeted therapy for at least 3 months. ETS was defined as the degree of tumor shrinkage at the first post-baseline radiological evaluation conducted 4–8 weeks after initiating second-line targeted therapy.

Results: Of these 271 patients, 26 had ETS from -100% to -50%, 70 from -49% to -25%, 84 from -24% to 0%, and the remaining 91 failed to achieve a reduction in the tumor size. The median OS following the initiation of second-line targeted therapy stratified from -24 to 0%, and the remaining 91 failed to achieve a reduction in the tumor size.

Conclusions: ETS at the first post-baseline assessment under treatment with a second-line targeted agent could serve as a useful parameter with an independent impact on OS in mRCC patients receiving second-line targeted therapy. Therefore, it is highly recommended to select second-line targeted agents that make it possible to induce primary tumor remission to further improve the prognosis of mRCC patients following the failure of first-line targeted therapy.

Legal entity responsible for the study: N/A
Funding: Japanese Society of the Promotion of Science
Disclosure: All authors have declared no conflicts of interest.

813P Correlation of longitudinal target-lesions sizes with progression-free (PFS) and overall-survival (OS) in 2nd line metastatic renal cell carcinoma: a retrospective analysis of AXIS trial

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Background: OS and PFS are commonly correlated with response upon RECIST criteria. Whether a more dynamic approach considering overall and individual lesions trajectories may be of predictive/prognostic value is worth investigating.

Methods: Target lesions size (TL) from AXIS trial (NCT00678392: axitinib (A) vs sorafenib (S) at baseline (bTL) and subsequent time-points up to 24 months were retrospectively analyzed. TL were grouped by major organs. Relationship between OS/PFS and TL was assessed using mean-trajectories and joint models (JM) with Cox/Weibull regression (C/W-R) including time to treatment interaction, with/without non-linear term. Mean trajectories obtained from unsupervised longitudinal clustering (ULC) were subject to C/W-R including S/A effect, age and IMDC risk group.

813P Efficacy of cabozantinib (cab) over everolimus (eve) by metastatic site and tumor burden in patients (pts) with advanced renal cell carcinoma (RCC) in the phase 3 METEOR trial

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Background: High tumor burden (TB) in pts with RCC is associated with poor prognosis (laccovielli JU Int 2012). In the Phase 3 METEOR trial (NCT01865747) in advanced RCC after prior vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) therapy (Choueiri TW URO 2015;105:145-46) cab significantly improved 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 < 0.001) compared with eve.

Methods: 658 pts were randomized 1:1 to cab (60 mg qd) or eve (10 mg qd). Stratification factors were MSKCC risk group and number of prior VEGFR TKIs. Endpoints included PFS, OS and ORR. Subgroup analyses by metastatic site and low and high TB (median ≤ median ≥ median sum of target lesion diameters [SOD] at baseline) are presented.

Results: At baseline, 74% of pts had visceral (lung or liver) metastases (mets); 63% had lung mets and 29% had liver mets. Median SOD at baseline was 65 mm (range 0–291) in the cab arm and 65 mm (0–258) in the eve arm. Subgroups by metastatic site and TB generally had similar baseline characteristics on both arms. High compared to low TB, was associated with fewer favorable (34% vs 57%) and more intermediate (47% vs 36%) and poor risk (19% vs 7%) pts per MSKCC criteria. For pts with visceral mets, the HRs favored cab (PFS HR 0.48, 95% CI 0.38–0.60; OS HR 0.66, 95% CI 0.52–0.85). These benefits with cabo were consistent across the metastatic sites analyzed (liver and lung). For pts with low TB, HRs for cabo vs eve were 0.63 (95% CI 0.47–0.84) for PFS and 0.76 (95% CI 0.54–1.08) for OS vs 0.41 (95% CI 0.31–0.54) for PFS and 0.60 (95% CI 0.45–0.80) for OS for pts with high TB. Median OS with cab was 22.0 mo for low TB and 18.1 mo for high TB vs 19.3 mo and 12.2 mo with eve, respectively. The most common grade 3 or 4 adverse events in these subgroups were consistent with the safety profile in the overall study population.

Conclusions: Treatment with cabo was associated with improved PFS and OS compared to eve in pts irrespective of tumor burden or metastatic site. Pts with high tumor burden appeared to have a stronger relative benefit with cabo compared to eve for both OS and PFS.

Clinical trial identification: NCT01865747
Evaluation of the novel “trial within a trial” design of METEOR, a randomized phase 3 trial of cabozantinib versus everolimus in patients (pts) with advanced renal cell carcinoma (RCC)

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Background: Comparative studies of time-to-event endpoints should be designed to yield a wide range of event times to accurately characterize the hazard function (HF) relationship and ensure valid hazard ratio (HR) estimates. The total sample size (N) is ideally small relative to the number of events needed for a time-to-event endpoint. A primary endpoint that is time-dependent is more easily analyzed than a treatment effect that is based on a time-independent endpoint. The primary endpoint of interest in METEOR was progression-free survival (PFS). A “trial within a trial” design was used to assess the primary endpoint of PFS in METEOR (NCT01865747) to confirm 259 events; the secondary overall survival (OS) endpoint required 408. As a result, the planned total N (650) was much larger than required to evaluate PFS. Shorter PFS times would be overrepresented if an event-driven analysis was conducted among all 650 pts, potentially undermining the ability to assess the proportional hazards assumption. To address this, the design of METEOR employed a novel “trial within a trial” design: PFS was analyzed in the first 375 randomized pts (PFS Pop), OS was analyzed in all 658 randomized pts (ITT Pop). Both populations follow the intention-to-treat principle.

Methods: To assess the impact of the design, PFS was reanalyzed at the date of the 24th event in the ITT Pop (minimum follow-up (min F/up) 2 days) and compared to both the primary endpoint results for 247 events in the PFS Pop (min F/up 11 mo) and supportive results for 394 events in the ITT Pop (min F/up 6 mo).

Results: The HPs were reasonably proportional between arms in all analyses. The HR and median estimate for the cabozantinib arm in the primary analysis of 247 events in the PFS Pop (0.38, 7.4 mo) are close to the estimates in the larger analysis of 394 events in the ITT Pop (0.52, 7.4 mo) using the same cutoff date. Despite the similar relationship among HPs, an analysis using an earlier cutoff (≤247 events) upon 247 events in the ITT Pop was biased, overestimating the treatment benefit as represented by the HR and underestimating the median PFS in the cabozantinib arm (0.49, 6.0 mo).

Conclusions: The “trial within a trial” design provided critical data required to characterize the HF relationship in METEOR and demonstrate robust results. This design should be considered when the HF relationship is unknown and the total N is large relative to the number of events needed for a time-to-event endpoint.

Clinical trial identification: NCT01865747

Legal entity responsible for the study: Exelixis, Inc.

Funding: Exelixis, Inc.

Results:
evaluate the potential prognostic ability of HR-QoL parameters on OS. Scores were in prognostic factor analysis. Cox proportional hazards regression was performed to 
COMPARZ study (NCT00720941) were analyzed retrospectively. Baseline 
MSKCC and IMDC risk classification scores consist of clinical and 
related quality of life (HR-QoL) has been previously shown to have prognostic 

Background: MSKCC and IMDC risk classification scores consist of clinical and laboratory parameters, which are able to classify patients prognosis. Baseline health related quality of life (HR-Qol) has been previously shown to have prognostic relevance in cancers. We therefore tested whether the addition of HR-Qol parameters to these tools can improve prognostic accuracy.

Methods: 1100 1st line patients treated with sunitinib or pazopanib within the 
to these tools can improve prognostic accuracy.

Conclusions: 

Table: 817P Univariable analysis on prognosis, adjusted for risk groups.

<table>
<thead>
<tr>
<th>HR-QoL</th>
<th>P</th>
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<tbody>
<tr>
<td>IMDC risk</td>
<td>FAVORABLE</td>
</tr>
<tr>
<td>FACIT-F</td>
<td>INTERMEDIATE</td>
</tr>
<tr>
<td>IMDC risk</td>
<td>CONTINUOUS</td>
</tr>
<tr>
<td>FKS1-19</td>
<td>FACIT-F</td>
</tr>
<tr>
<td>IMDC risk</td>
<td>INTERMEDIATE</td>
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<td>DRS-P</td>
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<tr>
<td>IMDC risk</td>
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<tr>
<td>IMDC risk</td>
<td>CONTINUOUS</td>
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</tbody>
</table>

Each HR-Qol parameter was statistically significantly prognostic for OS univariately (P < 0.001 for each) and remained significant after adjustment for risk categories of MSKCC and IMDC (Table). When adjusting FACIT-F (HR 0.99 (CI95% 0.97 - 1.00), P = 0.04) and DRS-P (HR 0.98 (CI95% 0.96 - 1.00), p = 0.072) for each other in a multivariable analysis, significance was borderline or lost. Spearman p for FACIT-F and DRS-P was 0.78, indicating a high level of correlation. Based on a priori defined cutpoints, median OS for patients with low/high FACIT-F: FKS1-19 and DRS-P was 14.2/33.6, 22/33.6 and 23.4/39.7 months respectively.

Conclusions: Our analyses indicate that baseline HR-QoL scores add to established risk prognosticators. However, only a single HR-QoL score should be used for further validation. Further study of discrimination ability is ongoing.

Clinical trial identification: NCT00720941

Legal entity responsible for the study: GSK sponsored clinical trial, which is the data

Funding: Medical School Hannover, Leibniz University; McMaster University

Disclosure: V. Grünwald: Honoraria: BMS, Novartis. Pfizer Consultation: BMS, Novartis. Pfizer. All other authors have declared no conflicts of interest.

Analysis of regional differences in the phase 3 METEOR study of cabozantinib (cabo) versus everolimus (eve) in advanced renal cell carcinoma (RCC)


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8Urology, Klinikum der Ludwig Maximilians-Universität München, Munich, Germany
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10Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA
11Urology, Klinikum Rechts der Isar der Technische Universität München, Munich, Germany
12Oncology, Escarpment Cancer Research Institute, McMaster Medical Centre, Hamilton, ON, Canada
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15Urology, University of Southern California, Los Angeles, CA, USA
16Medical Oncology, University of Miami, Florida, USA
17Genitourinary Medicine, Imperial College, London, UK
18Urology, University of Chicago, Chicago, IL, USA
19Genitourinary Medicine, Imperial College, London, UK
20Healthcare, GSK
21Consulting/Advisory: Pfizer, Roche, Novartis, Merck, Bayer, Eisai, Roche, Prometheus Labs Inc, BMS, Foundation Medicine Inc. Research Funding: Pfizer, GSK, Novartis, BMS, Merck, Exelixis, Roche, Asta/Zevara, Tracon, Peloton.

Background: In the METEOR study (NCT01865747), patients (pts) with advanced RCC and prior treatment with an antiangiogenic therapy were randomized to receive cabo or eve. Improved progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) were demonstrated in the cabo arm vs the eve arm (Choueiri 2016 JCO suppl abstr 4506). Baseline characteristics and clinical outcomes were evaluated in pts enrolled in three regions: Europe (EU; 19 countries), North America (NA; USA, Canada) and Asia Pacific (AP; Australia, South Korea, Taiwan).

Methods: 658 pts were randomized 1:1 to receive cabo (60 mg qd) or eve (10 mg qd). Stratification factors were MSKCC risk group and number of prior vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs).

Results: Of pts enrolled in METEOR, 339 and 246 came from EU, NA and AP, respectively. Baseline demographic characteristics other than race were similar between regions. Pts with 2 or more prior TKIs were more frequent in EU and NA (31% and 33%) than AP (17%). Prior use of axitinib was rare in AP (1%) compared to EU and NA (17% and 22%). PFS and OS in the cabo arm were prolonged vs eve in all regions, with PFS hazard ratios (HR) of 0.54, 0.50 and 0.43 and OS HRs of 0.67, 0.79 and 0.49 for EU, NA and AP, respectively. The cabo arm ORRs (% 95% CI) for EU, NA and AP regions were 15% (10-21), 16% (10-24) and 28% (15-45). Adverse event (AE) rates were generally similar across regions. Subsequent treatment with VEGFR-TKI and anti-PD-1/L1 agents was most frequent in NA and least frequent in AP, and at higher frequency in the eve arm versus the cabo arm. Posttrial use of eve in the cabo arm was similar across regions (Table).

Conclusions: Improvements in PFS, OS and ORR for cabo vs eve were measured across all regions in the METEOR trial despite differences in subsequent treatment. No differences in safety were reported.

Clinical trial identification: NCT01865747

Legal entity responsible for the study: Exelixis, Inc.

Funding: Exelixis, Inc.

**B1**P Real world outcomes of patients with metastatic renal cell carcinoma (mRCC) using first-line sunitinib or pazopanib: the Canadian experience


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3Medical Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada
4Medical Oncology, QEII Health Sciences Centre, Halifax, NS, Canada
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7Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada
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10Medical Oncology, Juravinski Cancer Centre, Hamilton, ON, Canada
11Medical Oncology, McGill University Health Centre The Montreal General Hospital, Montreal, QC, Canada
12Medical Oncology, CancerCare Manitoba MacCharlies, Winnipeg, MB, Canada
13Medical Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, ON, Canada
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Background: Standard first-line treatment for mRCC includes VEGF-targeted therapy. Clinical trial data has shown similar efficacy between sunitinib and pazopanib; however, a real world experience in Canadian patients is unknown. We aim to determine outcomes and compare toxicities of patients with mRCC treated with first-line sunitinib or pazopanib.

Methods: Data were retrieved from the prospective Canadian Kidney Cancer Information System (CKCis) database from January 2011 to November 2015. Patients with clear cell mRCC treated with first-line sunitinib or pazopanib were included. Time-to-Treatment Failure (TTF) and overall survival (OS) were calculated using Kaplan-Meier methods. Cox regression analysis was allowed for adjustment of International Metastatic RCC Database Consortium (IMDC) criteria and age was treated as a continuous variable. Fisher's exact tests were used to compare dose-modifying toxicities between the two therapies.

Results: Our cohort included 670 patients: 93 treated with pazopanib and 577 with sunitinib. Median TTF was greater in patients treated with sunitinib versus pazopanib (31.9 vs 20.6 mos, p = 0.028) and maintained significance (6.0 vs 3.7 mos, p = 0.046) and maintained significance when adjusted for IMDC criteria (HR 0.60, 0.38-0.95 95% CI, p = 0.028). Common toxicities requiring dose modification, including fatigue and diarrhea, were similar between both groups. However, patients treated with sunitinib had a significantly higher incidence of mucositis, hand-foot syndrome, and GERD; patients treated with pazopanib had a significantly higher incidence of liver toxicity and a trend towards weight loss.

Conclusions: In Canadian patients with clear cell mRCC, survival and treatment duration appears to favour sunitinib over pazopanib. Plausible explanations include potential differences in patient selection for pazopanib, the contemporary experience with individualized dosing on sunitinib, and small sample size. These data on real world toxicities are informative and may aid physicians and patients in guiding treatment decisions.

Legal entity responsible for the study: Canadian Kidney Cancer Information System (CKCis), Kidney Cancer Canada

**B1**P Sunitinib (2 weeks on/1 week off schedule) in metastatic renal cell carcinoma patients. Progression free and overall survival

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Background: The recommended schedule of sunitinib (SU) for metastatic renal cell carcinoma (mRCC) pts is 50 mg/day p.o. for 4 weeks and 2 weeks rest. The half-life of SU and its active metabolite is very slow: 40-60 and 80-110 hours, respectively. Given on several consecutive days the accumulation is 3-4 fold and 7-10 fold, respectively. The steady state concentration is achieved on days 7-10 and 10-14. 50 mg/day is enough to achieve the target concentration of ≥ 50 ng/mL. During the 14 days rest the concentration will decrease to the starting level. The correlation between the SU AUC and the time to progression is well known.

Methods: Based on the above in case of short term adverse events (AEs) we have applied the 2 weeks on/1 week off schedule instead of dose reduction.

Results: Altogether 130 mRCC pts (median age: 61 yrs, M/F: 91/39) were enrolled in the study: 121 (93%) pts were nephrectomized. 95 (123pts) had RCC histology: 67 (39%), 49 (38%) and 42 (32%) pts belongs to the intermediate and poor MSKCC prognostic groups, respectively. SU was the first-line treatment in 75 cases (58%), 34 (26%) had IFN and 21 (16%) patients had IL-2 treatment before. Patients received altogether 1617 cycles of SU (median 8, range: 1-68). 344 (range:56) cycles were given according to 4/2, and 1273 (1-18) according to 2/1 schedule, respectively. Upon progression on SU the following therapies were given: sorafenib (n = 10), azitidine (7), pazopanib (1), cabozantinib (1), everolimus (16). The median progression-free survival (mPFS) was: 13.5 (95%CI 12-16.5) mos and the median overall survival (mOS) was 30 (24-36) mos. If the 2/1 schedule was given in more than 2/3 of the total cycles (n = 83) the mPFS was 18 (13.5-28.5) mos and mOS was 18 (10-44) mos compared to those who had 2/1 schedule in less than 2/3 of the total cycles (n = 47) with mPFS 6 (4.5-9; P = 0.002) mos and mOS 11 (7-21). P = 0.001). Short-term AEs were as follows: fatigue: 41%; anorexia: 25%; mucositis: 33%; diarrhea: 37%; hand-foot syndrome 35%; hypertension: 30%. Although the AEs were quite frequent they lasted shorter and dose reduction had to be performed only in 12% (n = 16) during the 2/1 schedule.

Conclusions: Changing the SU 4/2 to 2/1 schedule instead of reducing the dose, was safe and resulted in a longer median progression-free and overall survival.

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Disclosure: All authors have declared no conflicts of interest.

**B1**P Tolerability associated with sunitinib (SU) 2-week on and 1-week off schedule (2/1 schedule) compared with its standard schedule in metastatic RCC (mRCC): Meta-analysis

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Background: SU is the 1st line standard treatment for mRCC and it requires 4-week on treatment and 2-week off as a standard schedule for mRCC. The treatment is associated with several adverse events (AEs), such as fatigue, hand-foot syndrome (HFS), neutropenia, thrombocytopenia etc. Schedule modifications of SU including 2/1 schedule are studied and the results provided the total number of treatment-related adverse events decreased in 2/1 schedule without compromising efficacy. However, the effect of 2/1 schedule on individual AEs was not clearly understood.

Methods: This analysis included 1 randomized controlled trial (RCT): Lee et al. 2015 (RESTORE trial, NCT00570882) and 4 non-randomized controlled studies (non-RCT): Nerl et al. 2013, Kondo et al. 2014, Brudarz et al. 2015 and Pan et al. 2015. The primary objective was to estimate risk of individual adverse events in SU 2/1 schedule versus standard one and secondary objectives were to evaluate efficacy

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Success: 7 AEs were evaluated with a standard data of RCT compared with the weighted meta-analysis data (non-RCT meta). Meta-analysis technique, including fixed effects modelling with Review Manager v5.3 was used to pool study-level data using the inverse-variance of each study as the weight. Data cut-off for this analysis: Apr 2015

Results: The selected studies included a total of 484 patients with mRCC, which comprised 74 and 410 from RCT and non-RCTs, respectively. The risk ratio of fatigue and neutropenia for 2/1 schedule vs. standard significantly decreased in both RCT and non-RCT meta (risk ratio (RR) of fatigue: 0.69 [95% confidence interval (CI) 0.51, 0.95] vs. 0.75 [0.63, 0.89], RR of neutropenia 0.60 [0.37, 0.99] vs. 0.58 [0.41, 0.83]). Other AEs also tended to decrease in both sets except diarrhea and anemia. Efficacy outcomes were comparable between 2/1 and standard schedule.

Conclusions: This meta-analysis suggests that 2/1 schedule of SU compared to its standard one decreases risk of fatigue and neutropenia and also favoured to control other AEs without compromising efficacy even with limited sources of data. A patient-level meta-analysis to confirm these findings is warranted.

Legal entity responsible for the study: Pfizer Pharmaceutical Korea Ltd.

Funding: Pfizer Pharmaceutical Korea Ltd.

Disclosure: H.J. Kang, S. Lee: Employee of Pfizer Pharmaceutical Korea Ltd.

Outcome of patients with multiple glandular metastases from renal cell carcinoma treated with targeted agents

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Background: Pancreatic metastases (PM) from renal cell carcinoma (RCC) are rare and have been associated with long-term survival. The purpose of this study was to evaluate the outcome of RCC patients (pts) with multiple glandular metastases (GM), defined as RCC metastasis to pancreas and at least one other gland including thyroid, parotid, adrenal, breast, ovaries or testes, treated with targeted therapies (TTs).

Methods: GM pts treated between 1993 and 2014 were retrospectively identified from a database of RCC pts with PM of 11 European centers. Survival of GM pts was compared with that reported in either PM pts and in a population of 330 mRCC pts with extraglandular metastases treated with TTs at Instituto Nazionale Tumori between 2006 and 2012 (control group). Overall survival (OS) was defined as the time from diagnosis of metastatic disease to death. Survival functions were estimated using the Kaplan–Meier method for left-truncated data and statistically compared using the log-rank test.

Results: Among 276 PM pts, 64 pts with at least one additional GM were evaluated. Median age was 64 yrs, sex ratio M:F was 42/22, 59 pts (92%) received prior nephrectomy. Fifty-six pts (88%) had at least 2 additional GM, 7 pts (11%) had at least 3 GM and 1 pt had 4 GM. GM were the only metastatic site for 4 pts (6%). After a median follow-up of 58.6 months (IQR 26.4-106.8 mo) median OS was 56.4 months (44%) revealed cytokines and 35 (56%) pts received subsequent lines of TTs. After a median follow-up of 51.6 months (IQR 27.6-63.6 mo) median OS was 80.4 months (95%CI 64.8-99.6 mo) for PM pts.

Conclusions: GM from RCC are associated with remarkable survival. Despite some limitations, these findings suggest that GM might be considered as a predictor of favorable prognosis. Sample collection for translational analysis would be critical to further characterize this rare metastatic pattern associated with a less aggressive disease.

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.
Long-term duration of axitinib treatment in advanced renal cell carcinoma

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Background: Axitinib is a selective, second-generation inhibitor of vascular endothelial growth factor receptors approved globally in advanced renal cell carcinoma (aRCC). A subset of patients (pts) treated with axitinib achieve long-term disease control. This analysis characterized the duration of treatment (DT) and clinical outcome of pts with aRCC who achieved a DT >18 months on axitinib therapy.

Methods: A retrospective analysis of data from 402 treatment-naïve pts with aRCC treated with axitinib in phase II (NCT00835978) or III (NCT00920816) clinical trials was conducted. Data on DT, objective response rate (ORR) per RECIST v1 criteria, and early tumor shrinkage (defined as ≥10% shrinkage at first scan) were compared between pts who had DT >18 months (longer DT) vs pts who had DT ≤18 months (shorter DT).

Results: Of the 402 pts, 152 (37.8%) had longer DT and 250 (62.2%) had shorter DT. Overall, 119 (29.6%) had DT > 2 years, 71 (17.7%) had DT > 3 years, and 28 (7.0 %) had DT > 4 years. The median (range) DT was 34.7 (18.4–177.1) months for longer DT vs 6.5 (0.1–77.1) months for shorter DT. ORR was 75% for longer DT vs 24.4% for shorter DT (difference, 50.6%; 95% CI 41.9–69.3%; p < 0.0001). More patients had early ≥10% tumor shrinkage in the longer DT group (74.8%) vs the shorter DT group (55.3%; difference: 19.6%; 95% CI, 10.2–29.0%; p < 0.0001). Grade 3 adverse events were more frequent in longer DT compared with shorter DT and included hypertension (25.0% vs. 14.8%), diarrhea (14.5% vs 4.4%), and weight decrease (11.2% vs 3.2%), respectively. ECOG performance status 0, platelet ≥150,000 (male: > 130,000 or female: > 115,000), no bone or liver metastases, and baseline tumor burden below overall median sum of longest diameter (96 mm) were associated with longer DT.

Conclusions: Among aRCC patients treated with first-line axitinib, a substantial proportion of patients remain on therapy for a prolonged period of time. Longer axitinib treatment duration (>18 months) is associated with increased ORR and proportion of patients remain on therapy for a prolonged period of time. Longer DT is associated with improved ORR and early tumor shrinkage. This was true for patients who had DT > 18 months (longer DT) vs patients who had DT ≤18 months (shorter DT). Analysis was conducted to identify baseline characteristics associated with longer DT.

Legal entity responsible for the study: Dr Jonathan Belsey
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Clinical outcomes and dosing patterns of 2nd targeted therapy in metastatic renal carcinoma: a retrospective chart review in the EU

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Background: This study evaluates the real-world outcomes and dosing patterns of metastatic renal cell carcinoma (mRCC) patients treated with everolimus (EVE), axitinib (AXI), and sorafenib (SOR), and as 2nd targeted therapy in Europe. We expanded the study to include patients from an additional country and updated the results presented at ASCO GU 2016 (4558).

Methods: Oncologists and urologists in the UK, Germany, France, and the Netherlands reviewed charts of adult mRCC patients who experienced disease progression on 1st targeted therapy with sunitinib or pazopanib and initiated 2nd targeted therapy with EVE, AXI, or SOR between 10/2012 and 6/2013. Overall survival (OS) and progression-free survival (PFS) and from the initiation of 2nd targeted therapies were evaluated using Kaplan-Meier analyses, and compared across cohorts using multivariable Cox proportional hazard models. Proportions of patients with dose adjustments and dose intensities relative to the recommended doses were also compared.

Results: A total of 309 charts were reviewed, with 115, 96, and 98 mRCC patients receiving EVE, AXI, and SOR as 2nd targeted therapy, respectively. Mean age was 60.2 years and 66.7% were male. The majority of patients received sunitinib as 1st targeted therapy (79.3%) and the rest received pazopanib (20.7%). No statistically significant differences were observed in OS or PFS after adjusting for patient characteristics [AXI vs. EVE: hazard ratio (HR) (95% CI): 1.22 (0.77-1.94) and 1.26 (0.81-1.95); SOR vs. EVE: HR (95% CI): 1.25 (0.75-2.10) and 1.47 (0.95-2.28)]. A significantly greater proportion of AXI-treated patients had a dose increase (AXI: 13.2% vs EVE: 6.0%; p < 0.01; vs. SOR: 0.0%; p < 0.01). Relative dose intensity was also significantly higher in AXI-treated patients (AXI: 1.02 vs EVE: 0.91; p < 0.01; vs. SOR: 0.98; p < 0.01).

Conclusions: In this retrospective study, no statistically significant differences in OS or PFS were observed among patients treated with EVE, AXI, and SOR. Rates of dose adjustment and dose intensities relative to the recommended doses were also compared.
escalation and relative dose intensities were significantly higher among AXI-treated patients compared to EVE- or SOR-treated patients.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

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Conclusion: In this real life population, the incidence of SSE was very high in mRCC pts with bone metastases. The combination of denosumab with anti-angiogenic drugs was associated with a high incidence of ONJ that may have been favored by dental extraction while on treatment. The present study underlines the need to improve strategies to prevent the onset of SSE in this population of pts.

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Everolimus-induced pneumonitis as predictor of outcome in patients with metastatic renal cell carcinoma

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Background: Previous research has shown that certain treatment related adverse events correlate with clinical efficacy of targeted therapies in the treatment of patients with metastatic renal cell carcinoma (mRCC). A well-known class effect of mammalian target of rapamycin inhibitors is non-infectious pneumonitis. We evaluated the possible association of pneumonitis with outcomes in mRCC patients treated with everolimus.

Methods: 303 consecutive patients with mRCC were treated in a single university hospital cancer center. We identified 85 patients (28.1%), who received sequential everolimus after first-line targeted therapy. Treatment-induced adverse events including pneumonitis were assessed and analyzed for the possible association with outcome using the Kaplan-Meyer method and Cox regression adjusted for known risk factors.

Results: 33 patients (38.8%) developed clinical symptoms and radiological findings of pneumonitis during everolimus treatment. In univariate analysis patients with pneumonitis had both a longer overall survival (OS) (19.67 vs. 8.50 months; P < 0.001) and progression-free survival (PFS) (4.17 vs. 3.27 months; P < 0.05) as compared to patients with no pneumonitis. Additionally, the overall best response was partial response or stable disease in 50.0% of patients with pneumonitis as compared to 26.6% of the patients with no pneumonitis (P < 0.05). In multivariate analysis adjusted for age, gender and Memorial Sloan-Kettering Cancer Center (MSKCC) risk score for previously treated patients, pneumonitis was significantly associated with a longer OS (adjusted HR, 0.45; 95% CI 0.26-0.77; P < 0.01). A similar pattern was seen for PFS although the result was not statistically significant (adjusted HR, 0.63, 95% CI 0.38-1.03, P = 0.06). Pneumonitis remained significantly associated with longer OS (adjusted HR, 0.47; 95% CI 0.27-0.81, P < 0.01) in a multivariable model with pneumonitis as a time-dependent covariate.

Conclusion: Our results suggest that pneumonitis may be associated with everolimus treatment efficacy. Further validation studies are warranted to confirm our findings.
Outcome of patients with metastatic chromophobe renal cell carcinoma treated with sunitinib

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Background: Metastatic chromophobe renal cell carcinoma (mchRCC). Data on its activity in the rare variant of metastatic chromophobe RCC (mchRCC), is limited. We aimed to analyze the activity of sunitinib in a relatively large and homogeneous international cohort of mchRCC patients, in terms of outcome and comparison to mccRCC.

Methods: Records from mmchRCC patients treated with first line sunitinib in 10 centers across 4 countries were retrospectively reviewed. Univariate and multivariate analyses of association between clinicopathological factors and outcome were performed. Subsequently, mchRCC pts were individually matched to mccRCC pts. We compared the clinical benefit rate (CBR), progression free survival (PFS), and overall survival (OS) between the groups.

Results: Between 2004-2014, 36 patients (median age 64, 67% male) with mchRCC were treated with first line sunitinib: 78% achieved a clinical benefit (partial response or stable disease). Median progression free survival (PFS) and overall survival (OS) were 24 months respectively. Factors associated with PFS were the HENG risk (HR >3.5, p = 0.03) and pre-treatment neutrophil to lymphocyte ratio (NLR) >3 (HR 0.63, p = 0.02). Factors associated with OS were the HENG risk (HR 4.1, p = 0.04), liver metastases (HR 3.8, p = 0.03) and pre-treatment NLR <3 (HR 0.55, p = 0.03). Treatment outcome was not significantly different between mchRCC patients and individually matched mccRCC patients. In mccRCC patients (p = value versus mchRCC), 72% achieved a clinical benefit and median PFS and OS were 9 and 17 months respectively.

Conclusions: In metastatic chromophobe renal cell carcinoma, sunitinib therapy may be associated with similar outcome and toxicities as in metastatic clear cell renal cell carcinoma. The HENG risk and pre-treatment NLR may be associated with PFS and OS.

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Retrospective analysis of metastatic non-clear cell renal carcinoma (NCCRC): the Spanish Grupo Centro Experience

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Background: Non-clear cell renal carcinoma (NCCRC) represents a group of multiple histologic subtypes, with different clinical outcomes and uncertain optimal treatment. Due to the infrequency of these histologies, they are usually grouped as one and treated the same way as clear cell renal carcinoma.

Methods: We performed a retrospective, multicenter study including patients (pts) with metastatic NCCRC diagnosed between 1995 and 2015. Data were collected from medical records at 14 hospitals. We evaluated the baseline clinical features, histologic subtypes, therapeutic management and survival status.

Results: We collected a total of 173 pts, with a median age at diagnosis of 65 years (24-90), 67.1% men, and 85.5% had undergone nephrectomy. Histologic subtypes were 55.5% papillary carcinoma, 13.9% chromophobe, 0.6% oncocytoma, 23.1% sarcomatoid and 6.9% unclassified tumours. Assignment according to MSKCC risk groups were: 21.4% favourable, 53.8% intermediate, 20.2% poor, 4.6% unknown. 62.4% pts received tyrosine kinase inhibitors (TKI) as first line (82.4% sunitinib, 9.3% pazopanib and 8.3% sorafenib). 11% mammalian target of rapamycin inhibitors (mTORi: 89.5% temsirolimus), 6.9% chemotherapy, 3.8% immunotherapy and 4% local treatment. Only 8.1% pts did not received any kind of treatment. Response rate (RR) in evaluable pts (142) were: complete 5.6%, partial 17.6%, stable disease 40.8% and progression in 35.9%. 59.5% pts had discontinued treatment due to progression and 13.3% due to toxicity. 90 pts received a second line of treatment, most of them TKI (93%). 30% pts were treated with everolimus. At the time of data cut-off (April 1, 2016), 125 pts had died, with a median overall survival (OS) of 11 months (1-73). OS according to histology: papillary 18 m, chromophobe 16 m, sarcomatoid 5m and unclassified 5m. Favourable prognosis NCCRC pts lived longer than intermediate or poor prognosis ones (32 m vs 11 m vs 5.5m).

Conclusions: Clinical outcome reported in this study shows lower RR and OS than previously published by other authors, probably due to the high percentage of sarcomatoid and poor prognosis tumours in this population. In view of these results, further research is needed in this area.

Legal entity responsible for the study: Spanish Grupo Centro
Results from 4 different risk-adapted surveillance strategies in a single Hospital for patients with stage I seminomatous germ cell tumours

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Background: Purpose: To describe treatment results in 4 cohorts of patients with stage I seminomatous germ cell cancer (SGCC) treated within 4 different risk-adapted surveillance strategies according to national guidelines.

Methods: From January 1, 1994, to December 31, 2015, 186 patients with stage I SGCC, were included in 4 different cohorts treated within different risk-adapted surveillance strategies: Group 1: 1994 to 1999, patients with T ≥ T1 received two cycles of carboplatin (CBDCA/x2), Group 2: 1999 to 2003, patients received CBDCAx2 if either tumour size ≥ 4 cm or rete testis invasion, Group 3: 2004 to 2009, patients received CBDCAx2 if both tumour size ≥ 4 cm and rete testis invasion were present, and Group 4, patients received CBDCAx2 if either tumour size ≥ 4 cm or rete testis invasion size ≥ 4 cm were present, two patients that received radiotherapy were included in Group 4. Follow-up consisted of serum tumour markers and physical exam every 3 months plus abdominal CT scans every 6 in the first two years, and at longer intervals thereafter.

Results: Disease-specifc survival: 100%. Three patients died, one because car accident, two patients due to metastatic colorectal and pancreatic cancer. Table summarize results by cohort. N CBDCA (relapse) Follow-up PSA (Sy) Platinum/ patient Group 1 38 8 (0) 30 (3) 92% 25, 0.67 Group 2 49 23 (1) 26 (3) 92% 58, 1.18 Group 3 52 18 (0) 34 (4) 91% 48, 0.92 Group 4 47 24 (3) 23 (3) 75% 42, 0.89 Relapse: All patients had good prognosis disease. Only one patient who progressed after 2 cycles of Carboplatin need ITP chemotherapy and finally High Dose Chemotherapy and he is currently free of disease 8 years later. A trend for a later relapse was observed in patients relapsing after being treated with carboplatin.

Conclusions: A risk adapted surveillance programme provided an overall specific survival of 100%. Relapse rate in patients receiving Carboplatin in 1 cycle seems to be higher than for patients included in protocols receiving Carboplatin x2. Then number of total (CBDMC + CBDP) was higher for the Groups with CBDCAx2. These results suggest that vascular invasion was a better predictor for selecting patients for adjuvant chemotherapy. This is unexpected, as the patients had no evidence of dissemination.

Legal entity responsible for the study: Oncology Service, Germ Cell Cancer Unit, Hospital Sant Pau

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Carboplatin dose based on actual renal function vs. dose capping: no excess of hematotoxicity in treatment of seminoma stage I

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Background: Single-dose Carboplatin (C) AUC7 is an adjuvant treatment option in Seminoma stage I. Many of these patients have very good renal function and hence high absolute doses of C are frequently administered. Some experts and clinical guidelines recommend capping of C dose at Creatinine-Clearance (Crea-CI) of 125 ml/min because of concerns of excessive toxicity. The rationale for these concerns has not been explored in patients with Seminoma stage I so far.

Methods: Analysis of a cohort of patients with stage I Seminoma treated with C AUC 7 in 2 Swiss centres 2005 – 2015. Main inclusion criteria: Normal blood count at treatment, no evidence of metastatic disease, first 8 weeks of follow-up. Comparison of incidence and grade (CTCAE v4.0) of hematological adverse events (AEs) in patients with Crea-CI < 125 ml/min without dose capping.

Results: 74 patients with 229 documented measurements were identified. Median age 41 years (Range 22 – 71), Crea-CI ( Cockcroft-Gault) 126 ml/min (70 – 206), C dose 1013 mg (700 - 1477). 12 patients with Crea-CI >125 ml/min and capped C dose (resulting in AUC <7) were excluded. In 35 patients with Crea-CI <125 ml/min a total of 74 AEs were documented, 81% were grade 1, compared to 61 AEs, 82% of them grade 1 (P< .89) in 27 patients with Crea-CI >125 ml/min and no dose capping. No statistically significant differences of AEs in patients with Crea-CI > vs. < 125 ml/min were noted. In each group one clinical relevant AE with subsequent interventions occurred: Febrile neutropenia in 1 patient in with Crea-CI <125 ml/min, 1 patient with Crea-CI >125 ml/min received one platelet transfusion (2.8% vs. 3.7%, P = .85).

For further details see table.

Table: 835P

<table>
<thead>
<tr>
<th>Crea-CI &lt;125 ml/min (N = 35)</th>
<th>Crea-CI &gt;125 ml/min &amp; no dose capping (N = 27)</th>
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<tr>
<td>Decreased Haemoglobin</td>
<td>71% (25) vs. 59% (15)</td>
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<tr>
<td>Decreased Platelet Count</td>
<td>57% (20) vs. 78% (21)</td>
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<tr>
<td>Decreased Platelet Count &lt;52</td>
<td>11% (4) vs. 29% (6)</td>
</tr>
<tr>
<td>Decreased White Cell Count</td>
<td>37% (13) vs. 48% (13)</td>
</tr>
<tr>
<td>Decreased Neutrophil Count</td>
<td>46% (16) vs. 44% (12)</td>
</tr>
<tr>
<td>Decreased Neutrophil Count &lt;2</td>
<td>26% (7) vs. 19% (5)</td>
</tr>
<tr>
<td>AEs with clinical interventions</td>
<td>2.8% (1) vs. 3.7% (1) platelet transfusion in case of neutropenia G4</td>
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</table>

Conclusions: Concerns of excessive toxicity in patients with Seminoma stage I and Crea-CI >125 ml/min treated with adjuvant C AUC7 are not supported by our data. Most AEs were grade 1 (>80%). There was also no statistically significant excess of AEs > grade 2. Therefore capping of C dose is not justified in this situation.

Clinical trial identification: BASEC Nr. 2016-00472

Legal entity responsible for the study: Kantonsspital St. Gallen, Switzerland, Dr Martin Fehr

Funding/ N/A

Disclosure: All authors have declared no conflicts of interest.

Outcome of patients with metastatic germ cell cancer treated between 2000 and 2013 at two centers in Munich

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Background: Treatment of metastatic germ cell cancer (GCC) is based on the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic classification published in 1997. 5-year survival rates were reported to be 91%, 79%, and 48% for patients with good, intermediate and poor prognosis, respectively. The question arises whether treatment results improved over time due to cumulative experience and whether there is still a need for dose intensification in intermediate and poor-risk patients.

Methods: The records of all patients (pts) with metastatic GCC treated at two institutions in Munich between 2000 and 2013 were reviewed with regard to time of initial diagnosis, histopathology, stage, tumor marker levels, metastatic spread, type and duration of chemotherapy (CT), and outcome. Progression-free survival (PFS) and overall survival (OS) were estimated with the Kaplan-Meier method. The Log rank test was used to compare survival distributions of different groups.

Results: Of 255 patients identified, 30 pts were excluded due to incomplete data. 189 of 225 pts (84%) included into the study were treated as outpatients and 36 (16%) as inpatients. The median age was 35 years, seminoma and nonseminoma were diagnosed in 72 (32%) and 153 (68%) pts, and 204 pts (91%) had a primary gonadal GCC. 175 (78%), 30 (13%) and 20 pts (9%) had good, intermediate and poor prognosis according to the IGCCCG classification system. The vast majority of pts received 3 to 4 cycles of platinum-based CT while primary high-dose CT was applied to 3 pts in the poor-prognosis group. The 2-year-PFS of pts with good, intermediate and poor prognosis was 91%, 83% and 37%, and the 3-year-OS was 98%, 96%, and 66%, respectively. There was no significant difference in the 5-year-OS between pts in the good and intermediate prognosis group.

Conclusions: Compared to data from the 1997 IGCCCG classification system, the outcome of pts with metastatic GCC has considerably improved. Notably, no significant differences in the 5-year-OS were observed between pts with good and intermediate prognosis. While the outcome of pts with intermediate-prognosis is excellent, treatment results in the poor-prognosis group are still unsatisfactory.

Legal entity responsible for the study: N/A

Funding: Ludwig-Maximilians-University Munich

Disclosure: All authors have declared no conflicts of interest.
Long-term changes in testosterone levels in testicular cancer survivors

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Background: Few studies have used serial measurements of total testosterone (TT) to evaluate long-term changes after testicular cancer treatment. We aimed to evaluate changes in TT after completion of a five or ten year follow-up programme.

Methods: From a long-term follow-up study of testicular cancer survivors (NCT02240966), 78 patients were included. Inclusion criteria were: Available post-treatment measurements of TT and luteinizing hormone (LH) within the follow-up programme (visit 1) and measurement of TT and LH after completion of follow-up (visit 2). Androgen substitution and age > 65 years at visit 2 were exclusion criteria. Patients were divided according to treatment: unilateral orchectomy + radiotherapy (14-20 Gy) due to contralateral germ cell neoplasia in situ (GCNIS) (n = 18), standard dose bleomycin, etoposide and cisplatin (BEP) (n = 19), retroperitoneal radiotherapy (Stage I) (n = 25), LH, TT and sexual hormone-binding globuline (SHBG) at visit 1 and visit 2 were compared within each treatment group with paired t-test.

Results: Time from treatment, age and reproductive hormones at visit 1 and visit 2 are presented in the table (median, interquartile range). TT declined in all treatment groups. In the GCNIS-group, 9/18 patients had TT levels < 10 nmol/l at visit 2. LH increased in the GCNIS-group while there were no significant changes in the other two groups. There were no changes in SHBG between visit 1 and visit 2.

Conclusions: Total testosterone declines after the completion of follow-up, irrespectively of treatment. TT is lowest in patients treated with radiotherapy due to contralateral GCNIS. Evaluation of testosterone levels should be continued beyond ten years in patients with GCNIS.

Clinical trial identification: NCT02240966

Legal entity responsible for the study: The Local Ethical Committee of the Capital Region of Denmark.

Funding: Copenhagen University Hospital Righospitalet

Disclosure: All authors have declared no conflicts of interest.

<table>
<thead>
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<th>Year from treatment</th>
<th>Visit 1</th>
<th>TT (nmol/l)</th>
<th>Visit 2</th>
<th>TT (nmol/l)</th>
<th>P-value</th>
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</thead>
<tbody>
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<td>0</td>
<td>68 (13.3-8.9)</td>
<td>5.6 (3.2-13.5)</td>
<td>5.3 (3.4-8.9)</td>
<td>1.2 (0.6-4.9)</td>
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<td>4.7 (1.2-9.0)</td>
<td>4.2 (2.1-10.2)</td>
<td>3.0 (2.4-5.9)</td>
<td>0.002</td>
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<tr>
<td>10</td>
<td>12 (6.5-15.0)</td>
<td>11.0 (4.3-18.3)</td>
<td>10.9 (4.5-18.2)</td>
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<td>Reference visit</td>
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<td>1.2 (0.6-2.5)</td>
<td>0.002</td>
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</table>

| LH (IU/l) | Visit 1 | 6.6 (4.5-8.7) | 6.6 (4.5-8.7) | 1.00 |
| Visit 2   | 7.0 (5.2-8.8) | 7.0 (5.2-8.8) | 1.00 |

| SHBG (nmol/l) | Visit 1 | 37 (29-47) | 37 (29-47) | 1.00 |
| Visit 2     | 32 (24-40) | 32 (24-40) | 1.00 |

Conclusions: Testosterone declines after the completion of follow-up, irrespectively of treatment. TT is lowest in patients treated with radiotherapy due to contralateral GCNIS. Evaluation of testosterone levels should be continued beyond ten years in patients with GCNIS.

Legal entity responsible for the study: The Local Ethical Committee of the Capital Region of Denmark.

Funding: Copenhagen University Hospital Righospitalet

Disclosure: All authors have declared no conflicts of interest.

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| LH (IU/l) | Visit 1 | 6.6 (4.5-8.7) | 6.6 (4.5-8.7) | 1.00 |
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| SHBG (nmol/l) | Visit 1 | 37 (29-47) | 37 (29-47) | 1.00 |
| Visit 2     | 32 (24-40) | 32 (24-40) | 1.00 |

Conclusions: Total testosterone declines after the completion of follow-up, irrespectively of treatment. TT is lowest in patients treated with radiotherapy due to contralateral GCNIS. Evaluation of testosterone levels should be continued beyond ten years in patients with GCNIS.

Legal entity responsible for the study: The Local Ethical Committee of the Capital Region of Denmark.

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Disclosure: All authors have declared no conflicts of interest.
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Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Funding: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Disclosure: All authors have declared no conflicts of interest.

840P Dacomitinib as first-line treatment of locally-advanced (LA) or metastatic penile squamous cell carcinoma (PSCC): Interim analysis of an open-label, single-group, phase 2 trial


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Background: The survival results of neoadjuvant or 1st-line chemotherapy (CT) for LA or metastatic PSCC are poor. HER pathway alterations may be a driver in a suitable therapeutic target in PSCC. An open-label, single-arm, phase 2 trial of 1st-line/ neoadjuvant Dacomitinib, an irreversible pan-HER tyrosine kinase inhibitor, is currently recruiting patients (pts, NCT01728233). The results of a planned interim analysis are presented.

Methods: 37 pts with chemonegative cN2-3 or M1 disease will receive Dacomitinib 45 mg daily until surgery or disease progression (PD)/unacceptable toxicity. Computed tomography and PET scan are repeated q2 months. Simon’s Optimal 2-stage design is applied. The primary endpoint (PE) is the objective response-rate (4ORR = CR/PR according to RECIST v1.1): H0 ≤5%, H1 20%, and β = 10% resulting in 1/4 responses required). Univariable Cox analyses were done. Next generation sequencing (NGS) with panel analysis from all pts is planned (Icahn, Life Technologies).

Results: From 06/13 to 02/16, 20 pts were enrolled (18 evaluable for response). Median age was 59 yrs (IQR: 54-78). 5 (25%) pts had a metastatic and 15 a LA-PSCC. At clinical staging, 9 (45%) had clinical pelvic nodes and 11 (55%) bilateral nodal disease. Five were confirmed PR (4ORR = 27.8%, 95% confidence interval [CI]: 9.7-53.3), 9 stable diseases and 4 PD. 11 pts (61%) had a PR. 10 pts underwent post-dacomitinib lymphadenectomy: 90% necrosis was seen in one patient. Median follow-up was 13.1 months, 6-month PFS was 37.9% (95%CI 20.2-71.1), 6-months OS was 85.7% (95%CI 69.2-100). No significant factor was found for PFS/OS. Skin toxicity was observed in 9 pts (2 Grade 1, 7 Grade 2-3 [CTCAE v4.03]). Grade 2 diarrhea in 2. Tissue from one PR pt harbored nonsense mutations in FRK617 (KRAS), PTEN (AT5), and TP53 (R273H, loss of function mutation) genes.

Conclusions: Dacomitinib is endowed with promising single-agent activity in PSCC. Pending the final results, the PE was already met. Translational results may provide insights into the targeting of HER pathway in PSCC. Preliminary data on molecular alterations linked to clinical benefit are being observed.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori

Funding: Fondazione IRCCS Istituto Nazionale dei Tumori

Disclosure: All authors have declared no conflicts of interest.

841P Micro-RNA and mRNA integrative analysis revealed MMP1 as a predictor of lymph node metastasis in penile carcinomas

H. Kuasne1, M.C. Barros-Filho1, A. Busso-Lopes1, F. Marchi1, M. Pinheiro1, P. Scarpelino-Netto1, J.U. Muthu2, A. Lopes1, G.C. Guimaraes3, E.F. Faria3, J. Torreri1, M.G. Arraradas1,4, E.F. Faría1, J. C.D.S. Trindade-Filho1, S.A. Drigo1, S.R. Rogatto1

1CIPE, AC Camargo Cancer Center, São Paulo, Brazil, 2Department of Pathology, Hospital De Cancer De Barretos Foundation Pico XII, Barretos, Brazil, 3Department of Urology, AC Camargo Cancer Center, São Paulo, Brazil, 4Research Institute of Urology, UNESP, Botucatu, Brazil, 5Clinical Genetic, Veja Hospital Sygehus Liljeholm, Vejle Sygehus Vejle, Denmark

Background: Penile carcinoma (PeCa), a relevant public health problem in poor and developing countries, has only recently been explored by genetic and epigenetic studies aiming to identify markers useful to the clinical practice. Herein, we aimed to integrate miRNA and mRNA profiles data to identify molecular drivers of PeCa development and progression.

Methods: miRNA expression profile (TaqMan Human MicroRNA Array v2.0; Applied Biosystems) and mRNA expression data (444K, Agilent Technologies) were assayed in 23 PeCa tissues and 12 non-neoplastic penile tissues (NPT). Integrated analysis was based on predicted and experimentally validated miRNA/mRNA interaction. RT-qPCR confirmed the data in an independent set of cases (PeCa = 36, NPT = 27).

Results: Eighty-one miRNA and 2,697 mRNA differentially expressed were identified comparing tumor and non-neoplastic tissues. Integrated data analysis revealed that 255 miRNAs were specifically regulated by 68 miRNAs. Eight miRNAs and 10 mRNAs were evaluated by RT-qPCR in an array-dependent and independent set of cases (PeCa = 36, NPT = 27), confirming the results. Molecular diagnostic classifiers including MMP1, MMP12 and PPARG transcripts were able to distinguish tumors from NPT with 92% of sensitivity and 88% of specificity. Similarly, three miRNAs (hsa-miR-31-5p, hsa-miR-224-5p, and hsa-miR-223-3p) revealed to have the potential to discriminate tumors from NPT (82% of sensitivity and 74% of specificity).

Interestingly, higher MMP1 expression levels were capable to predict lymph node metastasis more efficiently than clinical-pathological data. Growth factors related pathways, human embryonic stem cell pluripotency and matrix metalloproteinases were the main deregulated pathways in PeCa.

Legal entity responsible for the study: Silvia Regina Rogatto

Funding: FAPESP

Disclosure: All authors have declared no conflicts of interest.

8421P A multicentre, international, randomised, open-label phase 3 trial of avelumab + best supportive care (BSC) vs BSC alone as maintenance therapy after first-line platinum-based chemotherapy in patients with advanced urothelial cancer (JAVELIN bladder 100)

T. Powles1, P. Grivas2, J.B. Aragon-Ching3, Y. Fanour4, E.R. Kessler5, Y. Tomitaka6, D. Charubabari7, R.J. Laliberte8, M. Shnaidman9, D. Petrylak1

1Medical Oncology, Royal Free Hospital, London, UK, 2Medical Oncology, Cleveland Clinic, Cleveland, OH, USA, 3Medical Oncology, Inova Schar Cancer Institute, Fairfax, VA, USA, 4Medical Oncology, St. Luke’s Hospital & Health Network, Bethlehem, PA, USA, 5Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 6Urology, Nigata University Graduate School of Medical and Dental Sciences, Nigata, Japan, 7Research, Pfizer Inc., New York, NY, USA, 8Medical Oncology, Yale Cancer Center, New Haven, CT, USA

Background: Although first-line cisplatin-based chemotherapy prolongs survival in advanced urothelial cancer (UC), most patients (pts) progress within 8 months and no standard second-line therapies are currently available. Recent studies with anti-PD-L1 agents in pretreated UC have shown antitumor activity and promising survival compared with historical controls. Avelumab (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody that has shown an acceptable safety profile and clinical activity across a range of tumour types in a large phase 1b study. In an expansion cohort of pts with pretreated UC, treatment with avelumab resulted in a 16% objective response and 59% disease control rate. A phase 3 study (NCT02603432) has been initiated to determine if maintenance therapy with avelumab can prolong the benefit of first-line chemotherapy in pts with advanced UC.

Trial design: JAVELIN Bladder 100 is a phase 3, international, open-label trial of avelumab + best supportive care (BSC) compared with BSC alone administered as maintenance treatment for pts with locally advanced/metastatic UC whose disease did not progress after first-line treatment with 4-6 cycles of gemcitabine + cisplatin or gemcitabine + carboplatin. Other eligibility criteria include measurable disease prior to chemotherapy and adequate hematologic/organ function. Avelumab 10 mg/kg is administered every 2 wks as a 1 hr infusion. An estimated 668 pts will be randomized 1:1 and stratified based on best response to first-line chemotherapy and metastatic site. This trial has 2 co-primary populations: pts with PD-L1-positive tumours and all pts. The primary endpoint is overall survival and secondary endpoints include progression-free survival (PFS), objective response, safety, and symptoms/quality of life. Tumour response and PFS (RECIST v1.1) are assessed by blinded central review. Trial enrollment began in May 2016. *Proposed IIN.

Clinical trial identification: NCT02603432

Legal entity responsible for the study: N/A

Funding: Pfizer Inc.

Background: Sunitinib is a tyrosine kinase inhibitor approved in first line mRCC setting at the dose of 50 mg daily for 4 weeks followed by a pause of 2 weeks (schedule 4/6 50mg). Due to toxicity this schedule 4/6 50mg can induce up to 50% of sunitinib dose modification (reduction and/or interruption). Current recommendation in such case is to reduce the dose to 37.5 mg per day (schedule 4/6 37.5mg). Retrospective and prospective data highlight an alternative schedule: 2 weeks of treatment followed by one week of pause (schedule 2/3 50mg). SURF trial is set up to compare schedule 2/3 50mg to schedule 4/6 37.5mg when toxicity occurs.

Trial design: SURF [NCT02689167] is a prospective, randomized, open-label phase Ib study. Patients are included at sunitinib initiation while receiving schedule 4/6 50mg according to the Marketing Authorization Indication. When a dose adjustment of sunitinib is required, patients are randomized between arm A with schedule 4/6 37.5mg and arm B with schedule 2/3 50mg. Main eligibility criteria are patients with locally advanced inoperable or mRCC who are starting first line treatment with Sunitinib; with histologically or cytologically confirmed renal cancer clear cell variant or with a clear cell component and with Karnofsky performance status ≥70%. Primary objective is to assess the median duration of sunitinib treatment (DOT) in each group. Key secondary endpoints are progression-free survival, overall survival, time to randomization, objective response rate, safety, sunitinib dose intensity, quality of life and the description of main drivers triggering randomization. We hypothesized that schedule 2/3 50mg would result in an improvement in median DOT from 6 months to 8.5 months. It was estimated that 112 patients would be needed in each arm during 24 months. In order to take account the possibility of treatment discontinuation before randomization 248 patients are necessary. Study started in February 2016; at April 2016, 5 patients were enrolled. Update on trial enrolment kinetics will be shown during ESMO congress.

Clinical trial identification: NCT02689167; Trial protocol number 2015-002575-16

Legal entity responsible for the study: University Hospital of Besancon, France

Funder: Pfizer

Disclosure: G. Mouillet: Membership on an advisory board: Pfizer. Novartis Corporate-sponsor research: Pfizer. Novartis. F. Bonnetain: Amgen Lengene Roche (plus grant) Novartis (plus grant) Integrangen Jansen Ipsen Merck Serono Nestle Bayer Roche. A. Thiery-Vuillermot: Consulting: Pfizer, Novartis Funding: Pfizer. All other authors have declared no conflicts of interest.

Phase 3 study of avelumab in combination with axitinib versus sunitinib as first-line treatment for patients with advanced renal cell carcinoma (aRCC)


1 Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, 2 The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA, USA, 3 Department of Medical Oncology, Royal Marsden Hospital, London, UK, 4 Department of Cancer Medicine, Gustave Roussy Cancer Campus, University of Paris Sud, Villejuif, France, 5 Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands, 6 Department of Medicine, Medical University of Vienna, Vienna, Austria, 7 Department of Medical Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA, 8 Immuno-Oncology, Pfizer Inc., Milan, Italy, 9 Immuno-Oncology, Pfizer Inc., New York, NY, USA, 10 Department of Hematology and Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA

Background: Combining a checkpoint inhibitor with an anti-VEGF therapy is a promising treatment strategy for advanced renal cell carcinoma (aRCC). Avelumab (MSB0010718C) is a fully human IgG1 anti-PD-L1 antibody with clinical activity in treatment-naïve pts with aRCC. JAVELIN Renal 101, a randomized, multicenter, phase 3 study (NCT02664608) compares avelumab + axitinib vs sunitinib in treatment-naïve pts with aRCC.

Trial design: The primary objective is to demonstrate superiority of 1L avelumab + axitinib vs sunitinib monotherapy in prolonging progression-free survival (PFS). 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 ECOG PS (0 vs 1) and region (US vs Canada/Europe vs rest of the world). Pts receive either avelumab 10 mg/kg IV Q2W + axitinib 5 mg orally BID continuously (cycle length 6 weeks) or sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks off. Treatment is discontinued for unacceptable toxicity or if any 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 will be assessed by blinded independent central review. Secondary endpoints include overall survival, PFS by investigator assessment, objective response, duration of response, time to response, safety, tumour biomarker assessments, and patient-reported outcomes. Enrollment in this pivotal phase 3 trial began in March 2016. *Proposed INN

Clinical trial identification: NCT02684006

Legal entity responsible for the study: N/A

Funding: Pfizer Inc.


Ongoing phase 2 study of erdafitinib (JNJ-42756493), a pan-Fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, in patients (pts) with metastatic or unresectable urothelial carcinoma (M/UR UC) and FGFR gene alterations


1 Genitourinary Medical Oncology, University of Texas, MD Anderson Cancer Center, Houston, TX, USA, 2 Medical Oncology, Hospital Clinic de Barcelona, Barcelona, Spain, 3 Urology, Ghent University Hospital, Ghent, Belgium, 4 Medical Oncology, US Oncology Research and Rocky Mountain Cancer Centers, Aurora, CO, USA, 5 Clinical Oncology, Janssen Research & Development, Raritan, NJ, USA, 6 BioStatistics, Janssen Research & Development, Raritan, NJ, USA, 7 Translational Research and Biomarkers, Janssen Research & Development, Raritan, NJ, USA, 8 Clinical & Drug, Janssen Research & Development, Beerse, Belgium, 9 Clinical Oncology, Janssen Research & Development and Ludwig-Maximilians-Universität München, Neuss, Germany, 10 Gyn, GU and Skin Cancer Unit, Centro Integral Oncológico Clara Campal, Madrid, Spain

Background: European Society for Medical Oncology guidelines recommend cisplatin-based combination chemotherapy for M/UR UC; however, ~30% of pts cannot tolerate cisplatin. Following progression, the only European Medicines Agency-approved treatment is vinflunine, which offers modest survival improvement. FGFRs are involved in UC development, and ~10% of pts with metastatic UC have FGFR alterations. In a phase 1 trial of pan-FGFR (FGFR1-4) inhibitor erdafitinib in pts with advanced solid tumors, promising antitumor activity and manageable safety profile were observed, including 3 partial responses among 8 pts with UC (Tabernero et al. J Clin Oncol. 2015;33:3401-3408). Efficacy and safety of 2 erdafitinib dose regimens are being evaluated in an open-label, phase 2 study in M/UR UC pts with specific FGFR translocations or mutations.

Trial design: Pts must have measurable (Response Evaluation Criteria In Solid Tumors v1.1) M/UR UC and either progression following chemotherapy or relapse within 12 months of last dose of neoadjuvant/adjuvant chemotherapy. They may have received any number of prior lines of treatment, including immunotherapy. Those who are chemotherapy naïve must be cisplatin ineligible per protocol. Eastern Cooperative Oncology Group performance status ≤2 and adequate bone marrow, liver, and kidney function (creatinine clearance ≥ 40 mL/min) are required. Pts are excluded if they have baseline phosphate consistently above the upper limit of normal or uncontrolled cardiovascular disease. Pts are randomized to an intermittent (10 mg/d, 7 d on 7 d off) or continuous (6 mg/d) regimen, both orally administered in a 28-d cycle, until a dose regimen is selected, with a plan to treat ~110 pts at the selected dose. The primary end point is objective response rate. Progression-free survival, duration of response, overall survival, safety, biomarker, and pharmacokinetic assessments are secondary endpoints. Enrollment is ongoing at 107 sites in 13 countries (NCT02365597).
Clinical trial identification: NCT02366597
Legal entity responsible for the study: Janssen Research & Development, LLC
Funding: Janssen Research & Development, LLC
Disclosure: A. O. Siefker-Radtke:Received research funding from Janssen R&D, Beerse, Belgium. J.M. Burke: Participated in advisory boards or been a consultant for Gilead, Incyte, Takeda, Janssen, and Pfizer, and has received travel grant funds with TG Therapeutics. A. O'Hagan, A. Avudai, B. Zhong, A. Santiago-Walker, P. De Perre, S. Brookes-Mar: Employee of Janssen R & D and holds stock in Johnson & Johnson. All other authors have declared no conflicts of interest.

AstraZeneca

Funding:

Tumori

Legal entity responsible for the study:

Clinical trial identification:

EudraCT 2016-001688-35

Clinical trial identification: EudraCT 2016-001688-35

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori

Funding: AstraZeneca

Disclosure: All authors have declared no conflicts of interest.
and assessment. Surveillance cystoscopy will be performed 12 and 24 weeks after the commencement of chemoradiotherapy, and assess the rate of complete response to therapy. Patients will enter follow up with clinical assessment, cystoscopy and CT staging performed at intervals until close of study. The primary endpoint assessed will be safety, as defined by a satisfactorily low rate of unacceptable toxicity (G3-4 adverse events or failure of completion of planned chemotherapy and radiotherapy according to defined parameters). The secondary endpoint will be efficacy, as assessed by the proportion of patients achieving a best response of complete response based on the first two 12 and 24 week post chemoradiotherapy cystoscopic assessments. Exploratory analysis will include assessment of tumour histopathological, molecular, genetic and immunological parameters. It is expected that it will take two years to accrue the required 30 patients across 5 Australian centres

Clinical trial identification: NCT02662062

Legal entity responsible for the study: N/A

Funding: Australian and New Zealand Urogenital and Prostate Cancer Trials Group

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Disclosure: A.J. Weickhardt: Research support: Novartis Advisory board. Roche, Bayer, Novartis. All other authors have declared no conflicts of interest.

Pembrolizumab in patients with Bacillus Calmette Guérin (BCG)-unresponsive, high-risk non-muscle-invasive bladder cancer (NMIBC): Phase 2 KEYNOTE-057 study


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Background: Despite standard-of-care therapy with transurethral resection of bladder tumor (TURBT) and intravesical BCG instillation, a large percentage of patients with NMIBC have disease recurrence/progression. PD-L1 is widely expressed in urothelial tumors, providing a therapeutic rationale for targeting the PD-1/PD-L1 pathway in NMIBC.

Keynote-057 (NCT02625961) is an open-label, phase 2 study designed to evaluate the efficacy of the anti-PD-1 agent pembrolizumab (pembro) in patients with high-risk, BCG-unresponsive NMIBC.

Trial design: Eligible patients must be ≥18 years; have histologically confirmed diagnosis of high-risk, BCG-unresponsive NMIBC (high-grade Ta, T1, and/or carcinoma in situ [CIS] despite adequate BCG treatment); be ineligible for or have declined radical cystectomy; and have ECOG PS 0-2. Patients must have undergone ≥2 cystoscopic procedures with the most recent ≥8 weeks of study start, including complete TURBT (tissue sample must be available). Patients will receive pembro 200 mg Q2W for 24 months or until disease recurrence, progression, or unacceptable toxicity. Patients will be placed into cohorts by presence (cohort A) or absence (cohort B) of CIS based on tissue pathology at screening. Response will be assessed using cystoscopy and urine cytology every 12 weeks for the first 2 years, every 24 weeks for the next 2 years, and every 52 weeks thereafter. CT imaging will be used to assess for metastatic or nodal disease. At 18 months, patients with no evidence of disease may discontinue treatment. Low-grade Ta recurrence will not be considered treatment failure; these patients may undergo repeat TURBT and remain on treatment. AEs will be monitored throughout the study and for 30 days after end of treatment (90 days for serious AEs and events of clinical interest) and graded per CTCAE v4.0. Primary end points will be overall survival and disease-free survival. The sample size will be 17 patients per cohort (consisting of the 3 + 6 patients). Following this safety period, up to a total of 36 evaluable patients will be recruited into the phase II part of the trial in the frame of a Simon-two-stage design. Pathological tumor response based on central pathology review is the primary endpoint. The null hypothesis, which is defined as a true response rate of 25%, will be tested against a one-sided alternative. In the first stage, 17 patients will be accrued. If there are ≥2 responses in these 17 patients, the study will be continued to full recruitment to a total of 36 patients. The null hypothesis will be rejected if ≥14 responses are observed in 36 patients, with a type I error rate of 0.05 (one-sided) and a power of 0.8 when the true response rate is 45%. Further endpoints are the radiological response and progression (RECIST 1.1), cancer-specific survival, quality of life and safety. A translational research program aiming at the identification of predictive biomarkers will accompany this clinical trial.

Clinical trial identification: EudraCT 2016-000081-33

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Pfizer Fabre GmbH

Disclosure: A. Hegele, G. Gakis: Pfizer Fabre. Advisory Role, Honoraria, Research Funding. C-H. Ohlmann: Pierre Fabre. Advisory Role, Honoraria. All other authors have declared no conflicts of interest.

TRAXAR study: a randomized phase 2 trial of axitinib and TRC105 versus axitinib alone in patients with advanced or metastatic renal cell carcinoma (mRCC)

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Background: Resistance to VEGF-targeted therapy is a major challenge in the contemporary treatment of mRCC, and endogenic activation may be an important mechanism leading to resistance. Endoglin is an essential angiogenic receptor expressed on proliferating tumor vessels and RCC stem cells, and is upregulated following VEGF inhibition. TRC105 is an endoglin monoclonal antibody that potentiates the anti-tumor activity of bevacizumab and VEGF receptor tyrosine kinase inhibitors in preclinical models. 18 patients were enrolled in phase 1b trial and, TRC105 dose escalation proceeded from 8 mg/kg (n = 3) to 10 mg/kg (n = 15) without dose limiting toxicity. TRC105 at its RP2D of 10 mg/kg was well tolerated with axitinib (A) 5 mg BID in RCC patients. Dose escalation of A to 10 mg BID was possible with the RP2D of TRC105. In phase 1b, the combination of TRC105 and A demonstrated preliminary evidence of activity, including partial responses in 29% of patients by RECIST 1.1, and longer PFS than expected with A as a single agent. The overall disease control rate (CR/PR/SD > 2 months) was 88% (15 of 17). Median PFS was 8.4 months, and was 9.6 months among patients with clear cell RCC. Adverse events characteristic of each drug were not increased in frequency or severity when the two drugs were administered concurrently, and most commonly included edema, diarrhea, fatigue, headache, and gingival bleeding.

Legal entity responsible for the study: Novartis, Pfizer, Genentech, Urogen, RMS Corporate-sponsored research. Novartis, BMS, Amgen. All other authors have declared no conflicts of interest.

JaNED – A phase Ib/II study assessing the neo-adjuvant combination therapy of vinflunine (VFL) with cisplatin (CDDP) followed by radical cystectomy (RC) in patients with muscle-invasive bladder cancer (MIBC)

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Background: Neo-adjuvant chemotherapy (CTx) prior to RC leads to a significant improvement in 5-year survival in MIBC. Guidelines recommend CDDP based CTx. However, the optimal regimen is still controversial and no standard has been defined so far. VFL, as a single agent, has proven clinical activity in urothelial carcinoma. VFL and CDDP mediate complementary mechanisms of action and their combination may provide a relevant benefit in the neoadjuvant setting.

Trial design: Systemically untreated patients with MIBC, clinically staged as T2-T4a (cT2-4a, cM0) and with an ECOG performance status of 0-1 will be enrolled in this

Legal entity responsible for the study: Novartis GmbH

Funding: Pierre Fabre GmbH


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Trial design: Phase 2 is a multicenter study that is actively enrolling at this time across approximately 30 sites in the US. In phase 2, 150 patients are randomized 1:1 to A +/- TRC105. Key inclusion criteria: 1 prior VEGF inhibitor, clear cell RCC, ECOG ≤ 1; one prior mTOR and one prior immune therapy is allowed. Primary endpoint is PFS and secondary endpoints are ORR, disease control rate, and to characterize the pharmacokinetic profile of TRC105 and A (NCT01806064).

Clinical trial identification: Protocol # 105RC101 (NCT01806064)

Legal entity responsible for the study: TRACON Pharmaceuticals, Inc. Lead PI: Toni Choueiri

Funding: TRACON Pharmaceuticals, Inc.


852TiP The PAZOREAL non-interventional study to assess efficacy and safety of pazopanib and everolimus in the changing metastatic renal cell carcinoma (mRCC) treatment landscape


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Background: Renal cell carcinoma (RCC) is diagnosed in about 15,500 patients per year in Germany, with up to 60% of patients requiring systemic treatment in the metastatic setting. Vascular endothelial growth factor receptor (VEGFR) and mammalian target of rapamycin (mTOR) inhibitors are broadly used in mRCC therapy and sequential first-line pazopanib (VEGFR inhibitor) and second-line everolimus (mTOR inhibitor) is a standard treatment option. Nivolumab was recently approved in Europe for use after previous therapy. The non-interventional PAZOREAL study is designed to observe the real-world use of first-line through third-line therapy in the evolving treatment environment.

Trial design: This is a prospective, non-interventional study that will evaluate the efficacy, tolerability, safety, and quality of life (QoL) in patients with mRCC treated with first-line pazopanib, second-line nivolumab or everolimus, or third-line everolimus after nivolumab. Adults with histologically confirmed mRCC of any subtype, who have a life expectancy of at least 6 months, and whose systemic treatment will either start with first-line pazopanib or continue with third-line everolimus after second-line nivolumab, are eligible. Treatment will follow the respective German drug labels. Patients’ history, treatment, disease assessment, concomitant medication, adverse events, follow-up treatments, and survival will be documented. Variables will include the time on drug for documented therapies, overall survival, dosing parameters, safety, and QoL (assessed by EQ-5D-5L questionnaire). Recruitment of patients started in December 2015 and is planned to end in December 2018, with a goal of 450 documented patients at about 150 sites in Germany. Four interim analyses are planned and the first analysis will be performed in April 2017. Immediately after approval of nivolumab in Germany, the study was opened for documentation of therapy sequences including in-label nivolumab treatment in the second-line setting.

Legal entity responsible for the study: Novartis Pharma GmbH

Funding: Novartis Pharma GmbH


853TiP Phase I/II dose-finding, safety and efficacy study of radium-223 dichloride in renal cell carcinoma patients with bone metastases


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Background: Presence of bone metastases (BM) is a factor of poor prognosis in metastatic renal cell carcinoma (mRCC). Radium-223 is a bone targeted active short half-life a-emitter approved in prostate cancer. Its activity in mRCC-ostelosarcoma is unknown.

Trial design: The proof of concept study EIFFEL is a French multicentric phase I/II designed to assess the value of Radium-223 for treatment of mRCC bone lesions. Main objective is to identify the most-successful dose among 4 activity levels: 27.3, 55, 82.5, 110KBq/kg. Primary endpoints are the 6 weeks dose-limiting toxicity (DLT) for escalation cohort and conditional efficacy upon whole-body MRI (WB-MRI) and NaF-PET scan for expansion cohort. In order to optimize the dose results, 4 innovative methods were implemented in a context of early phases: 1) a continual reassessment model is used for the 2 phases and expected to provide an optimal dose (most efficient activity given the acceptable toxicity) 2) Radium-223 to DLT causal relationship assessment uses an intrinsic imputability score to avoid confounding adverse events for DLT qualification, 3) a modified RECIST for bone lesions upon WB-MRI and NaF-PET (considering the entire bone metastatic burden) is used to monitor efficacy in the expansion cohort and 4) efficacy data gathered during the escalation phase will provide prior hypothesis to define the optimal efficacy threshold for the expansion cohort. Analysis of correlations between Radium-223 biodistribution scintigraphy, longitudinal WB-MRI, NaF-PET, and circulating bone remodeling markers will further address important questions in clinical, imagery, metabolism and nuclear medicine domains. The EIFFEL study should provide a large amount of useful data for evaluation and treatment of bone metastasis in mRCC. Results of phase I are expected Q1 2018 and Q4 2019 for final phase II results.

Clinical trial identification: EURACT # 2014-003774-16 - CODE: EIFFEL

Legal entity responsible for the study: ARTIC - Association pour la Recherche des Therapeutiques Innovantes en Cancérologie Siecle social : Service de Cancérologie Médicale Hôpital Européen Georges Pompidou 20-30, rue Leblanc, 75908 Paris Cedex 15

Funding: Bayer Healthcare

Disclosure: All authors have declared no conflicts of interest.
gynaecological cancers

Results of a phase 2 trial of selinexor, an oral selective inhibitor of nuclear export (SINE) in 114 patients with gynaecological cancers


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Background: The nuclear export protein Exportin 1 (XPO1) mediates the nuclear export of regulatory proteins including tumor suppressor proteins (TSP). XPO1 is expressed in aggressive ovarian carcinomas & is related to poor patient outcomes [Noske 2008]. In addition, mutations in XPO1 are common in patients (pts) with endometrial cancer [TCGA database]. Selinexor (SEL), a first-in-class inhibitor of XPO1, induces nuclear retention & activation of TSPs. This phase 2 trial evaluated the efficacy & tolerability of SEL in pts with metastatic ovarian (OC), cervical (CC) & endometrial (EC) cancers.

Methods: Eligible pts ≥18 of prior chemotherapy, ECOG PS 0-1. In OC, pts were platinum-refractory or resistant. EC & CC pts had at least one prior chemotherapy line for relapsed disease. Pts were grouped into cohorts by disease type & treated with single agent SEL. Three randomized treatment schedules (50 mg/m2 (BIW); 35 mg/m2 BIW; & 25 mg/m2 QW) were evaluated. Responses (RECISTv1.1) were evaluated every 2 cycles by RECISTv1.1, and safety by CTCAEv4.0 per cycle. The primary endpoint is overall response rate (ORR). Simon’s two-stage design was used.

Results: 66 OC (median 6 (1–11) prior treatment regimens [PTRs]), 23 EC (median 2 (1–5) PTRs) & 25 CC (median 3 (1–8) PTRs) were enrolled. DCR: OC: 49%; EC: 43%; CC: 24%. ORR: OC: 14%; EC: 14%; CC: 4%. Median PFS in OC: 11 wks, EC: 12 wks & CC: 6 wks. Sixteen pts (12 OC, 2 EC & 2 CC) were on SEL treatment >6 mos. The presence of CTGs in pts prior to treatment seem to be correlated with shorter PFS opposed to pts without CTGs. Common Grade 1 drug-related adverse events (AEs) for all 3 cohorts included nausea (56%), anorexia (47%), weight loss (44%) & fatigue (42%). Grade 3 drug related AEs included thrombocytopenia (11%), fatigue (10%), anemia (9%) & nausea (8%). Grade 4 AEs were cardiovascular (1%) & hyponatremia (1%).

Conclusions: Single agent SEL has anti-tumor activity in pts with heavily pre-treated OC & EC, but was lower in CC. SEL-associated toxicity is manageable. Combination studies are ongoing & phase 3 trials in OC & EC are being planned.

Clinical trial identification: Edradur CT 2013-20130650-24, NCT02005985

Legal entity responsible for the study: Karyopharm Therapeutics

Funding: Karyopharm Therapeutics


A phase 2 study of the cell cycle checkpoint kinases 1 and 2 inhibitor (LY2606368, Prexazertib) monohydrate in sporadic high-grade serous ovarian cancer (HGSO) and germline BRCA mutation-associated ovarian cancer (gBRCAm-OCva)

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Background: Checkpoint kinases 1 and 2 (CHK1/2) are the primary cell cycle regulators in tumors with p53 dysfunction, such as HGSO. The second-generation CHK1/2 inhibitor, LY2606368 showed preliminary activity in advanced cancer pts in phase 1 studies. We hypothesize that LY2606368 will result in clinical benefit in subsets of pts with HGSO.

Methods: Eligible pts had recurrent HGSO with negative BRCA testing or negative family history of hereditary breast and ovarian cancer syndrome (cohort 1) or a documented deleterious germline BRCA1/2 mutation (cohort 2); good end organ function and safety biopsiable disease, ECOG PS 0-2. Pts received LY2606368 monotherapy at 105 mg/m2 IV every 14 days per 28day cycle. Response was assessed every 2 cycles by RECISTv1.1, and safety by CTCAEv4.0 per cycle. The primary endpoint is overall response rate (ORR). Simon’s two-stage design was used to rule out 5% ORR in favor of an ORR of 25% (alpha = 0.10; beta = 0.10). If ≥2 responses are seen in 24 pts (12.5%), this would be sufficient to warrant further study.

Results: 22 women (15 HGSO/ 7 gBRCAm-OCva) have been treated (median age 61 (36–81)). The median number of prior therapies was 5 (1–13) for cohort 1 and 7 (3–12) for cohort 2. PR (median duration of response, 9 mos (3–90)) have been seen in 13 evaluable cohort 1 pts (ORR 38%), both with platinum-sensitive and three with platinum-resistant disease. Four of 6 evaluable cohort 2 pts attained SD 24 mos (median 4.5 mos), with ≥6 responses. Grade 3 or 4 treatment-emergent AEs include neutropenia (91%; 20/22), thrombocytopenia (27%; 6/22), febrile neutropenia (9%; 2/22) and diarrhea (9%; 2/22). Grade 3 or 4 neutropenia on day 8 resolved within 7 days in 13/22 pts. 13 pts received growth factor support due to febrile neutropenia or to avoid treatment delays.

Conclusions: LY2606368 alone shows promising preliminary activity in BRCA wild type HGSO pts and continues to enroll. Prophylactic use of G-CSF should be considered. Paired tumor biopsies and blood samples are being collected to examine potential biomarkers of response.

Clinical trial identification: NCT0203513

Legal entity responsible for the study: National Cancer Institute, NIH, Rockville, MD, USA

Funding: This work was funded by the Intramural Program of the Center for Cancer Research, NCI, National Institutes of Health, USA.

Disclosure: All authors have declared no conflicts of interest.
Results: Median age was 59 years; median number of prior chemo regimens was 2. Median duration of treatment was 6.9 months. The investigator-assessed confirmed objective response rate (RECIST v1.1) was 54% in pts with ≥2 prior chemo regimens. The median duration of investigator-assessed confirmed response was 9.2 months (95% confidence interval: 6.6–11.7). Common treatment-emergent adverse events included asthenia/fatigue (78%; grade ≥3: 15%), nausea (76%; grade ≥3: 4%), anemia (51%; grade ≥3: 27%), vomiting (50%; grade ≥3: 4%), and transient increased ALT/AST (47%; grade ≥3: 13%). Five pts died as a result of disease progression.

Conclusions: Rucaparib has clinical activity and an acceptable safety profile in pts with BRCA1/2-HGOC who received ≥2 prior lines of chemo. The efficacy of rucaparib will be compared to standard chemo in a phase 3 study (ABRREIA).

Clinical trial identification: NCT01482715 (NII), NCT01891344 (NII)

Legal entity responsible for the study: Clovis Oncology, Inc.

Funding: Clovis Oncology, Inc.


The predictive value of the CA-125 modeled kinetic parameter KELIM is validated in 3 independent datasets (AGO-OVAR 7 & 9; ICON 7 AGO/GINECO/GCIG trials)


Background: Mathematical modeling can be used to analyze longitudinal CA125 kinetics, and predict treatment efficacy. The modeled CA-125 elimination parameter KELIM was a predictive factor of efficacy in CALYPSO trial (You et al. Gynecol Oncol 2013). The present study aims at validating the independent predictive value of KELIM in phase III trial datasets with different 1stline treatments.

Methods: Data from AGO-OVAR 7 (carboplatin-paclitaxel (CP) +/- topotecan, n = 1388), AGO-OVAR 9 (CP +/- gemcitabine, n = 1742) and ICON-7 trials (CP +/- bevacizumab; French dataset only, n = 196) were analyzed. The biggest AGO 9 dataset was used as a training set, while AGO 7 & ICON7 were used as validation sets. CA125 concentration-time profiles was fit with following parameters: tumor growth rate (BETA); CA 125 tumor production (KPROD); CA 125 elimination rate (KELIM) & treatment indirect effect (Emax relationships) (BETA*KELIM) * (1 - (A/(A + A50))) – KELIM (CA125) where t is time. The predictive value of KELIM dichotomized by the median was tested regarding progression free survival (PFS) after other reported prognostic factors (stage; pathology; surgery/ completeness if any; grade; arms; Rustin) using Cox-models.

Results: Individual CA125 profiles were well described by the model in training and validation datasets, as validated by visual predictive checks. KELIM (β = 0.098) exhibited strong independent predictive value regarding PFS in training dataset (univariate: 24.0 vs 11.3 months, P < 0.001; multivariate: HR = 0.67, C95% 0.58-0.76), and in validation data (AGO-OVAR 7 dataset (univariate: 28.9 vs 11.1 months, P < 0.001; multivariate: HR = 0.58, C95% 0.40-0.83) & ICON-7 dataset (univariate: 37.5 vs 14.7 months, P < 0.001; multivariate: HR = 0.65, C95% 0.44-0.96). KELIM predictive value was consistently significant using multivariate tests against reported prognostic factors, and higher than Rustin cutoff.

Conclusions: The independent predictive value of KELIM was reproducible in large 3 datasets of ovarian cancer patients treated with different regimens. This may be a novel predictive factor, helpful for early selection of the best candidates during drug development.

Legal entity responsible for the study: Benoit You

Disclosure: All authors have declared no conflicts of interest.

The CHIVA study: a GINECO randomized double blind phase II trial of nintedanib versus placebo with the neo-adjuvant chemotherapy (NACT) strategy for patients (pts) with advanced unrescetable endometrial cancer (OC). Report of the interval debulking surgery (IDS) safety outcome


Background: The CHIVA study: a GINECO randomized double blind phase II trial of nintedanib versus placebo with the neo-adjuvant chemotherapy (NACT) strategy for patients (pts) with advanced unrescetable endometrial cancer (OC). Report of the interval debulking surgery (IDS) safety outcome

Results: Between January 2011 and February 2016, 60 eligible pts were included. Median age was 68 years (range 53-85). Previous treatment included pelvic radiotherapy (58%), chemotherapy (90%) and hormonal therapy (43%). Forty-five out of sixty pts were treated for at least four weeks, and were thus evaluable for the primary endpoint. Twenty-six of the evaluable patients (58%) had no progression at three months, with median PFS and OS of 5.3 and 9.5 months, respectively. The most common severe adverse events were gastrointestinal toxicity in 21% of 60 participants, including 2 patients with a gut perforation, one fatal gastrointestinal hemorrhage, one enterocutaneous fistula and one fatal enterovaginal fistula. Peritoneal disease existed in 80% of patients with severe gastrointestinal toxicity. A definite correlation with previous radiotherapy could not be established.

Conclusions: Pazopanib showed encouraging 3 months PFS in AEC. There may be a correlation between previous treatments and/or disease site with rare but severe gastrointestinal toxicity that has yet to be elucidated.

Clinical trial identification: NTR3139 (Dutch Trial Register), Registration date 15-NOV-2011

Legal entity responsible for the study: Academic Medical Center Amsterdam for Dutch Gynaecologic Oncology Group

Funding: Dutch Gynaecologic Oncology Group and Novartis Oncology

Disclosure: All authors have declared no conflicts of interest.

A DGGQ open-label multicenter phase II study of pazopanib in metastatic and locally advanced hormone-resistant endometrial cancer

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Background: There is a pressing need for second-line systemic treatment for metastatic, recurrent and/or locally advanced endometrial cancer (AEC) after hormonal therapy or chemotherapy. We studied the effect of the selective multi-targeted receptor tyrosine kinase inhibitor pazopanib on progression free survival (PFS) at three months for patients with AEC.

Methods: In this prospective phase II open label study, patients were recruited from six oncology departments in the Netherlands. Eligible patients had histologically or cytologically confirmed AEC, documented progressive disease and a WHO performance status of ≤ 2. All patients received treatment with pazopanib 800 mg once daily until progression, unacceptable toxicity or patient refusal. Dose reductions for toxicity were allowed. Patients were evaluable for the primary endpoint of PFS if at three months and if they had received pazopanib for at least four weeks. All participants were analysed for toxicity and overall survival (OS). The study was powered to demonstrate 50% PFS at 3 months (vs 38% based on previously reported studies) with α = 0.05 and β = 0.80.

Results: Between January 2011 and February 2016, 60 eligible patients were included. Median age was 68 years (range 53-85). Previous treatment included pelvic radiotherapy (58%), chemotherapy (90%) and hormonal therapy (43%). Forty-five out of sixty pts were treated for at least four weeks, and were thus evaluable for the primary endpoint. Twenty-six of the evaluable patients (58%) had no progression at three months, with median PFS and OS of 5.3 and 9.5 months, respectively. The most common severe adverse events were gastrointestinal toxicity in 21% of 60 participants, including 2 patients with a gut perforation, one fatal gastrointestinal hemorrhage, one enterocutaneous fistula and one fatal enterovaginal fistula. Peritoneal disease existed in 80% of patients with severe gastrointestinal toxicity. A definite correlation with previous radiotherapy could not be established.

Conclusions: Pazopanib showed encouraging 3 months PFS in AEC. There may be a correlation between previous treatments and/or disease site with rare but severe gastrointestinal toxicity that has yet to be elucidated.

Clinical trial identification: NTR3139 (Dutch Trial Register), Registration date 15-NOV-2011

Legal entity responsible for the study: Academic Medical Center Amsterdam for Dutch Gynaecologic Oncology Group

Funding: Dutch Gynaecologic Oncology Group and Novartis Oncology

Disclosure: All authors have declared no conflicts of interest.
to increase response rate to chemotherapy both in first-line (ICON7) and in relapse (OCEANS and AURELIA). Due to concerns about bevacizumab impact on ODS wound healing, the safety and efficacy of nintedanib, an orally available anti-VEGF/PDGFR/ FGFR tyrosine kinase inhibitor with a short half-life was explored in the neo-adjuvant setting.

Methods: All patients underwent laparoscopy and their disease was considered as unresectable (impossibility to achieve C0 at primary surgery). Eligible patients were randomized (2:1) to receive 3 cycles of NACT before ODS and 3 cycles of chemotherapy after ODS with carboplatin + paclitaxel and nintedanib or placebo (at cycle 182, 586 and at maintenance therapy as single agent during 2 years). The aim of ODS was to achieve C0. Surgical complications were scored according to Clavien-Dindo classification.

Results: A total of 188 patients were included and 121 (64%) patients underwent ODS (49 in placebo arm and 72 in experimental arm). Pts characteristics are well balanced between both arms. No significant difference was observed between the placebo and the nintedanib arm in terms of operating procedure duration (360 vs 330 minutes) and per-operative (18 vs 13%) complications. Bleeding (2 vs 9% of the pts), blood losses (506 vs 675 ml), and transfusion rate (12 vs 26% of the pts) were slightly less frequent in the placebo arm. Around half of the patients experienced at least one per-operative complication: 53% versus 47% in the placebo and nintedanib arm respectively. They were mostly of grade I-II (86% grade I-II, 14% grade III-IVa) with no significant difference between the placebo and the nintedanib arm. Post-operative complications, mostly of grade I-II were mostly observed in the first 30 days post-ODS.

Conclusions: Compare to placebo, the addition of the anti-VEGF nintedanib to neo-adjuvant chemotherapy did not significantly increase the rate of per-operative and post-operative complications of the interval debulking surgery.

Clinical trial identification: NCT01583322

Legal entity responsible for the study: ARCAGY-GINECO

Disclosure: All authors have declared no conflicts of interest.

Clinical trial identification: NCT01739218

Legal entity responsible for the study: Roche

Funding: Roche

Disclosure: R. Rouzier: Advisory board. S. Gouy, F. Selle, C. Pomel, E. Chereau, P. Cottu, F. Joly: Board Y. Ghazi, J. Dupin: Employee. All other authors have declared no conflicts of interest.

Results: Stage 1A analysis included 85 IPS and 65 DPs pts, median age 59 years and 64% stage IIIIC/IV disease. Stage 1B included 87 further DPs pts (total DPs = 152), median age 62 years, 92% stage IIIC/IV. Protocol treatment completion was high (90% vs 80% (p=0.03)). Complete resection rate at IDS was scheduled 28 ±7 days after the last neoadjuvant treatment course. The primary objective was to assess whether the CRR was significantly higher than the previously reported reference rate. Adding Bev to neoadjuvant CP achieved an expected but >80% 1A and >75% 1B pts received 6 cycles of platinum chemotherapy.

Achieved platinum dose intensity (mg/m2/week)

Conclusion: Completion of 6 cycles of platinum chemotherapy was high; however, protocol-defined q3w regimens were frequently modified. Protocol treatment completion differed significantly between arms in stage 1A, but not 1B, perhaps reflecting q3w paclitaxel toxicity in DPs patients. Rates of clinically relevant toxicity were acceptable, and despite aggressive dosing thresholds febrile neutropenia was rare. No dose modifications were implemented following stage 1A and 1B analyses, but early use of Bev was not associated with differences in toxicity. Most common reason for not completing protocol treatment was toxicity. G3+ toxicity was more frequent in stage 1A, probably due to upconcomitant neutropenia.

Table: 861P

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>Stage 1A</th>
<th>Stage 1B</th>
<th>Stage 1A</th>
<th>Stage 1B</th>
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<td>Toxicity</td>
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<tr>
<td>G1/G2+ Neutropenia, %</td>
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<td>G1/G2+ Diarrhoea, %</td>
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<tr>
<td>G1/G2+ Thrombocytopenia, %</td>
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<tr>
<td>G1/G2+ Tiredness, %</td>
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<tr>
<td>G1/G2+ Nausea, %</td>
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<td>G1/G2+ Vomiting, %</td>
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Conclusions: Completion of 6 cycles of platinum chemotherapy was high; however, protocol-defined q3w regimens were frequently modified. Protocol treatment completion differed significantly between arms in stage 1A, but not 1B, perhaps reflecting q3w paclitaxel toxicity in DPs patients. Rates of clinically relevant toxicity were acceptable, and despite aggressive dosing thresholds febrile neutropenia was rare. No dose modifications were implemented following stage 1A/1B analyses, but early use of G-CSF was recommended. PFS results are expected in Q2 2017; OS in 2018.

Clinical trial identification: ISRCTN10356387; EudraCT 2010-022209-16

Legal entity responsible for the study: Medical Research Council

Funding: Cancer Research UK

Disclosure: All authors have declared no conflicts of interest.
Hormonal therapy for epithelial ovarian cancer: a systematic review and meta-analysis of phase II studies

A. Decensi1, M. Provansal1, G. Freyer1, D. Berton-Rigaud2, E. Kalbacher3, O. Cojocarasu4, M. Fabbro5, J. Cretin6, Disclosure: All authors have declared no conflicts of interest. Italian Association for Cancer Research (AIRC) Funding: Legal entity responsible for the study: for a prognostic value of hormone receptors in EOC, our findings support the trend by year of study.

Results: The analyses encompassed a total of 39 phase II trials including 1,690 patients. Overall, we obtained a PES = 0.35 [95% CI, 0.21-0.50] for tamoxifen, 0.41 [95% CI, 0.21-0.58] for tamofoxen, 0.14 [95% CI, 0.05-0.28] for the anti-androgen flutamide, 0.50 [95% CI, 0.31-0.69] for tamoxifen plus goserelin, 0.52 [95% CI, 0.32-0.72] for the ER downregulator fulvestrant, even though the last three categories included on only one study each. The PES was better in studies including patients with ER +ve or PgR +ve disease [PES = 0.43, 95% CI, 0.34-0.52] compared with hormone receptor -ve patients [PES = 0.17, 95% CI, 0.09-0.24] or mixed [PES = 0.31, 95% CI, 0.17-0.46] disease. High tamoxifen doses (>20 mg/d) exhibited a worse PES = 0.36 [95% CI, 0.16-0.57] than the standard dose of 20 mg/d (PES = 0.50 [95% CI, 0.30-0.67]). A slightly better response was noted in platinum resistant [PES = 0.35, 95% CI, 0.19-0.50] vs platinum sensitive patients [PES = 0.43, 95% CI, 0.30-0.57]. There was no evidence for a response trend by year of study.

Conclusions: The activity of endocrine therapy in advanced EOC looks promising but has not adequately been evaluated in definitive clinical trials. Given the recent evidence for a prognostic value of hormone receptors in EOC, our findings support the implementation of randomized trials in hormone receptor positive EOC.

Legal entity responsible for the study: E.O. Galliera Funding: Italian Association for Cancer Research (AIRC) Disclosure: All authors have declared no conflicts of interest.

Non pegylated liposomal doxorubicin (npld, myocet) + carboplatin (cb) in patients (pts) with ovarian cancer in late relapse (oril): a phase 2 gineco study


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Background: CB + peglpetal iposplomoxorubicin (PLD) is standard in OCLR. Because of recurrent P.D. shortage, we explored the efficacy and tolerance of CB-NPLD Methods: From 11/2012 to 07/2014, 86 pts have been enrolled and treated at dose levels 1 (n = 3) and 2 (n = 6), all pts were evaluable for safety and response. Median age was 61 years (range, 49–73); median number of previous regimens was 3 (range, 1–4). GOOG score performance status was 0 (6 pts) or 1 (3 pts). No dose-limiting toxicities have been reported at either dose level, thus the RPD2 is CRLX101 15 mg/m2 (every other week) and paclitaxel 80 mg/m2 (3 weeks on/1 week off). Treatment-related adverse One of the most important is toxicities were neutropenia (9/9, 100%) and fatigue (6/9, 67%). There were no grade 3 or 4 treatment-related adverse events. However, all pts gained 3 or more kg. The only grade 3 adverse event was neutropenia.

Conclusions: CRLX101 given every other wk in combination with wkly paclitaxel has demonstrated early signs of antitumor activity and has been generally well tolerated to date in pts with platinum-resistant OC.
Background: Platinum-based chemotherapy represents the standard of care after surgery for OC, improving survival in patients (pts) with newly diagnosed advanced OC and in pts with recurrent platinum-sensitive disease. About 10-15% of OC pts has a germline mutation in BRCA 1/2 genes. Patients with BRCA mutation have a better prognosis and response to platinum-based therapy. Hypersensitivity reactions (HSRs) to chemotherapeutic agents are common and can limit their use: HSRs to carboplatin have been reported in about 15-20% of women. The aim of our study was to evaluate the incidence of HSRs to platinum compounds and other antineoplastic agents (taxanes, lansoprazole anticholinergics) in BRCA-mutated OC pts.

Methods: Patients eligible for analysis were OC pts treated in Our Center from 2010 to 2015. We retrospectively collected data regarding histopathological type, treatment, HSRs and genetic testing results. We assessed the correlation between incidence of HSRs and BRCA mutation status. The analysis was performed by Fisher exact test or Chi-square test for categorical variables.

Results: Out of 60 OC eligible pts, BRCA was evaluated in 32 pts. Among them, 16 had a pathogenic BRCA mutation (9 pts with a BRCA2 mutation, 6 pts with a BRCA1 mutation and 1 pts with both BRCA1 and BRCA2 mutations), in 16 patients genetic testing resulted negative. In pts with BRCA-mutated OC, a significant increase in HSRs to drugs was observed [11/16 (68%) vs 4/16 (25%), p < 0.03]. Looking at the group of patients who developed HSRs to platinum-based compounds (10 total cases of HSRs in both groups, 9 in BRCA-mutated pts and 1 case in BRCA wild-type (wt) pts), a significantly higher incidence of HSRs was observed in the group of BRCA-mutated pts [9/14 (64%) vs 1/13 (8%), p < 0.004].

Conclusions: Our analysis suggests that BRCA mutated OC pts might have an increased incidence of HSRs compared to BRCA wt pts. This might be due to a repeated exposure to platinum-based compounds or to an increased immune reactivity in this group of pts. If confirmed, these data may complicate the use of PARR-inhibitors in BRCA-mutated pts, registered only for relapsed OC pts in repeated exposure to platinum-based compounds or to an increased immune reactivity.

Legal entity responsible for the study: The study was coordinated by Clinica di Oncologia Isp.A.Medica

Funding: This study was performed in AOU Clinica di Oncologia Medica without any external funding

Disclosure: All authors have declared no conflicts of interest.

Impact of age on the safety and efficacy of bevacizumab (BEV)-containing therapy in patients (pts) with primary ovarian cancer (OC): Analyses of the OTILIA German non-interventional study on behalf of the North-Eastern German Society of Gynaecological Oncology Ovarian Cancer Working Group

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Background: The efficacy and tolerability of front-line BEV combined with carboplatin- or paclitaxel-based (CP) chemotherapy for first line OC has been demonstrated in randomised phase III trials. To assess the safety and effectiveness of first-line BEV-containing therapy in the real-world setting in Germany, we initiated the single-arm non-interventional OTILIA study. The latter part of OTILIA focused on elderly pts. We report the second interim analysis.

Methods: Pts with FIGO stage IIIb–IV OC received front-line BEV + CP according to the EU label. Adverse events were recorded at each cycle and graded using CTCAE v4.0. Investigators assessed response according to local practice. Exploratory analyses compared safety and efficacy according to age.

Results: Between Feb 2012 and Jan 2016, 713 pts from 200 centres received BEV-containing treatment for the EU label. More pts aged ≥70 vs ≥71 years had ECOG PS 0 (44% vs 28%, respectively) and fewer had comorbidities at baseline (57% vs 73%; hypertension in 31% vs 54%). There was little difference in FIGO stage between subgroups but overall tumour resection was more common in younger than older pts (31% vs 22%). At data cut-off (Jan 2016), PFS events had been reported in 278 pts (39%). The table shows key results. In exploratory multivariable Cox regression analysis including age, ECOG PS, FIGO stage, residual disease and ascites as covariates, viable residual disease (p=0.0001) and ascites >500 ml (p = 0.001) but not age (p = 0.4) were significant prognostic factors for PFS.

The socioeconomic burden of ovarian cancer in Spain

L. Delgado-Ortega1, A.G. Domínguez2, C. Moya-Alarcón1, Á. Hidalgo3

13Clinica di Oncologia Medica-AOU Ospedali Riuniti, Università Politecnica delle Marche, Ancona, Italy, 23Clinica di Oncologia Medica, Ospedali Riuniti-Ancona, Università di Ancona, Ancona, Italy, 3Clinica di Oncologia Medica and Centro Regionale di Genetica Oncologica, AOU Ospedali Riuniti Ancona Università Politecnica delle Marche, Ancona, Italy

Background: Ovarian cancer (OC) has relatively low prevalence and incidence rates in Spain (11.1 and 10.2 per 100,000 women per year, respectively), but is the second most frequent gynaecological cancer and the sixth leading cause of cancer death in Spain. Survival is related to the diseases stage at time of diagnosis. Epithelial OC represents 90% of total OC cases. Its economic burden in Spain was previously unknown.

Methods: We developed a Markov model from a social perspective simulating the natural history of epithelial OC and its four stages, with a 10-year time horizon, 3 week cycles, 3% discount rate, and 2015 €. Healthcare resource utilization and costs were estimated by disease stage. Direct healthcare costs (DHC) included early screening, genetic counselling, medical visits, diagnostic tests, surgery, chemotherapy, hospitalizations, emergency services, and palliative care. Direct non-healthcare costs (DNHC) included formal and informal care. Indirect costs (IC) included labour productivity losses due to temporary and permanent leaves, and premature death.

Epidemiological data and resource use in all stages were taken from the literature and validated for Spain by the Ovarcost group (a Spanish multidisciplinary advisory board) using a Delphi process.

Results: The total cost of epithelial OC over 10 years was €2,469 million: €278 million (11%) in stage I, €1,412 million (6%) in stage II, €1,478 million (60%) in stage III and €572 million (23%) in stage IV. Mean total cost per patient per year was €30,098: €9,723 (32%), €42,508 (€44,798 in stages I to IV). Of total costs, 69% were due to DHC, 28% to DNHC and 3% to IC. DHC were €162 million in stage I, €82 million in stage II, €99 million in stage III and €487 million in stage IV. Mean DHC per patient per year was €21,419. DNHC were €650 million in stage I, €52 million in stage II, and €490 million in stages III and IV, respectively. Mean DHC per patient per year was €7218.

Conclusions: Epileptic OC imposes a significant burden on the national health system and society as a whole in Spain. Investment in better early diagnosis techniques may increase survival and patient quality of life, which would likely reduce costs of late stages, leading in turn to a substantial reduction of the economic burden associated with OC.

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Table: 867P

<table>
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<th>Parameter</th>
<th>Age &lt;70 years</th>
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<tr>
<td>Median BEV duration, months (95% CI)</td>
<td>13 (12.2–14.1)</td>
<td>13.1 (11.3–13.8)</td>
</tr>
</tbody>
</table>

Main reasons for BEV discontinuation, n (%)a

- Disease progression | 72 (17) |
- Side effects | 29 (7) |
- Treatment-related adverse event | 5 (1) |
- Pt request | 8 (2) |
- Death | 20 (5) |
- End of documentation period | 54 (13) |

Grade 3/4 adverse events

- All | 1 (32) |
- Leading to BEV discontinuation | 30 (7) |

All-grade adverse events

- Hypertension | 70 (16) |
- Proteinuria | 18 (4) |
- Gastrointestinal perforation | 5 (1) |

Median PFS, months (95% CI)b

- All pts (n = 713)b | 22.6 (21.3–23.9) |
- No visible residual disease subgroup (n = 193) | 27.9 (25.1–NE) |
- Visible residual disease subgroup (n = 325) | 19.2 (16.0–21.3) |

868P

Direct effects of platinum-based chemotherapy ± bevacizumab on the bone metabolism of patients with primary and platinum-sensitive recurrent subovarian carcinoma

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Conclusions: The analysis of bone markers over time revealed significant changes in bone metabolism of patients receiving platinum-based chemotherapy ± bevacizumab. These findings suggest that the combination of chemotherapy and bevacizumab has a potential impact on bone health in patients with subovarian carcinoma.

869P

Vascular endothelial growth factor (VEGF) polymorphisms and outcome of epithelial ovarian cancer patients

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Conclusions: The results of this study suggest that VEGF polymorphisms may have a predictive and prognostic role in the outcome of ovarian cancer patients. Further studies are needed to confirm these findings in larger and more diverse patient cohorts.

870P

Prognostic and predictive significance of VEGF and TNFα levels in ascites of patients with epithelial ovarian cancer. Correlation with lymphocytes subpopulations


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Conclusions: The correlation between VEGF and TNFα levels in ascites and lymphocyte subpopulations may provide additional information on the response to anti-angiogenic therapy in ovarian cancer patients. Further studies are needed to confirm these findings in larger patient cohorts.
higher VEGF production than the remaining alleles. We aimed to analyze herein the roles of these SNPs in outcome of EOC patients.

Methods: Our analysis included 85 EOC patients seen at diagnosis seen from 1996 to 2007 (median age: 53 years; tumor of type I: 56, type II: 29; tumor at stage I: 37, stages II to IV: 48). Patients were treated with tumour resection and cisplatin-based chemotherapy. DNA from peripheral blood was analyzed by real-time polymerase chain reaction for genotyping of the polymorphisms. Progression free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and curves were compared by the log-rank test. The Cox hazards model was used to identify prognostic variables influencing survival in univariate analysis, and significant results were validated using a bootstrap resampling study to investigate the stability of risk estimates (1000 replications).

Results: As of Dec 15, 2015, 12 pts with ECOG PS 0/1 (50%/50%) and median age of 61 y (range 39-72) were evaluable for safety. 11/12 received chemotherapy. DNA from peripheral blood was analyzed by real-time polymerase chain reaction for genotyping of the polymorphisms. Progression free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and curves were compared by the log-rank test. The Cox hazards model was used to identify prognostic variables influencing survival in univariate analysis, and significant results were validated using a bootstrap resampling study to investigate the stability of risk estimates (1000 replications).

Results: At baseline, 22.2% of pts had low baseline CA125 levels vs pts who progressed. There were no Gr 4 or 5 related AEs or deaths. 5 pts (15.5%) had 2 lines of therapy. Atezo demonstrated tolerable safety and encouraging clinical activity. Scientifically rational combinations with chemotherapy, DNA from peripheral blood was analyzed by real-time polymerase chain reaction for genotyping of the polymorphisms. Progression free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and curves were compared by the log-rank test. The Cox hazards model was used to identify prognostic variables influencing survival in univariate analysis, and significant results were validated using a bootstrap resampling study to investigate the stability of risk estimates (1000 replications).

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Outcomes of clinical testing for tumor BRCA1 and BRCA2 gene analysis for 354 patients: first experience with tumor companion diagnostic for PARP inhibitors

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Background: Ovarian cancer patients with deficiencies in the DNA repair pathway have shown to have a higher probability to respond to PARP inhibitors. Pathogenic mutations in the genes BRCA1 and BRCA2 lead to defects in the DNA repair pathway. It has been shown that the prevalence of mutations in the BRCA genes is higher in the tumor cells than in germline. Thus, a tumor-based test could identify a higher number of potential patients.

Methods: This study assessed 354 consecutive individuals undergoing BRCA1 and BRCA2 full sequencing and large rearrangement analysis of DNA derived from FFPE tumor tissue in a DAKS accredited laboratory in Munich, Germany from Jan 2015 through April 2016. The tumor-based BRCA test consists of sequencing and large rearrangement analyses of the BRCA1 and BRCA2 genes using next generation sequencing (NGS). The large rearrangements are detected by NGS dosage analysis to determine copy number abnormalities indicative of deletion or duplication analyses.

Results: Of the 354 analyzed samples, 93 (26.5%) tested positive for a laboratory classified pathogenic mutation. 57 were found in BRCA1 and 37 in BRCA2. One specimen contained a pathogenic mutation in both BRCA1 and BRCA2. Due to different quality and age of the tumor samples, large rearrangement analysis could not be completed in 24 cases (6.8%). VUS rate in the analyzed tumors was 4.2%. Of the pathogenic mutations detected, 93.6% were sequencing variants and 6.4% were large rearrangements. Overall cancellation rate due to insufficient tumor, insufficient DNA, incorrect tumor type or other cancellation reasons is less than 5% in the observed timespan of 16 months.

Conclusions: The current study demonstrates that a robust diagnostic platform can detect BRCA-related mutations in ovarian tumors. While the quality of samples received into a commercial laboratory is quite variable, a positive rate of over 26% and an overall success rate (result generated) of over 91% indicates that tumor BRCA testing should be considered for ovarian cancer patients. In addition, a small but significant number of large rearrangements indicates that tumor BRCA testing should include dosage analysis for large rearrangements.

Legal entity responsible for the study: Myriad GmbH

Funding: Myriad GmbH


Impact of genomic heterogeneity and mutation patterns on the outcome of patients with epithelial ovarian cancer (EOC)

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Background: EOC often display genomic heterogeneity and mutations associated with homologous recombination repair deficiency (HRD), which may have prognostic/predictive relevance. In the present study, we examined the mutational evolution in EOC and its association with patient outcome.

Methods: We examined coding mutations in 306 paraffin tissue samples from 69 patients with stage III-IV EOC treated with standard chemotherapy. The samples (2-9 per patient) were from normal and tumoral epithelium (N), primary tumors (P) and metastatic sites (M). Coding regions in 39 EOC-related genes were sequenced at high depth (mean 2739, median 2362) and a genomic heterogeneity index (HGI) was calculated. Progression-free survival (PFS) was the clinical endpoint.

Results: In 64/69 patients, at least 2 paired N and M samples shared 640 mutations (16% of all mutations) in 15 genes. Shared mutations (s-mut) exhibited higher allelic frequency as compared to private ones (all p < 0.001). S-mut were found up to 60% in HRD genes (21% BRCA1, 37% BRCA2) and up to 25% in TP53. BRCA1 and BRCA2 s-mut prevailed in paired N/N, P/P and N/M; TP53 s-mut prevailed in paired P/P and M/M. Higher HGI was associated with absence of any s-mut (p = 0.017) and BRCA1 s-mut (p = 0.043) in paired N/P and with presence of TP53 s-mut in P/M (p = 0.018).

In patients with serous EOC, median PFS was 25.3 vs. 13.9 months for those with high HGI (n = 31), compared to those with low HGI (n = 13, log-rank p = 0.024); no association was observed for non-serous tumors (interaction p = 0.08). Among patients with BRCA1 low HGI, those with BRCA2 s-mut in paired N/P (n = 5) did not progress in 120 months, while patients without BRCA2 s-mut had median PFS of 18 months (n = 11, p = 0.001). Among patients with BRCA2 low HGI, those with high TP53 s-mut in paired N/P (n = 20) had worse PFS than those with low HGI (n = 5, p = 0.001), while in patients without BRCA2 s-mut no difference in PFS was detected.

Conclusions: A temporal mutation order in the evolution of EOC is suggested. HRD mutations seem important in the transition from normal to primary tumor and TP53 mutations in metastatic spread. Genomic heterogeneity seems to interact with tumor histology and shared normal/tumor HRD mutations for patient prognosis. Validation in larger patient series is needed.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group

Funding: Astra-Zeneca S.A.

Disclosure: All authors have declared no conflicts of interest.

A phase 1 study of single agent veliparib in Japanese subjects with advanced solid tumors


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Background: Veliparib (V) is a potent, orally bio-available PARP inhibitor that inhibits DNA damage repair. Up to 50% of high-grade serous ovarian cancer (HGSOC) is considered to have deficiencies in homologous recombination and thus be particularly sensitive to PARP inhibition. V has single-agent activity in HGSOC, as well as in BRCA-mutated breast, pancreatic or prostate cancers. The objectives of this study were to determine the recommended phase 3 dose (RPTD) of V monotherapy, to assess pharmacokinetics (PK) and to evaluate preliminary efficacy in Japanese subjects with HGSOC or other BRCA mutated cancers.

Methods: Tolerability was assessed in 2 dose cohorts (200 mg and 400 mg BID) on Days 1 - 28 of a 28 day cycle), and an expansion cohort (400 mg BID). Subjects continued to receive V until PD or predefined discontinuation criteria were met. Adverse events (AEs) were reported according to CTCAE Ver. 4.03. PK parameters were analyzed. Tumor response was measured by RECIST 1.1 and tumor markers including CA-125.

Results: A total of 16 subjects treated were all female, with a median age of 59 yrs (range 43 - 83). All but 1 subject with BRCA mutated breast cancer were with HGSOC. All had prior surgeries and chemotherapies (range 1 - 7). The most common treatment emergent AEs were nausea and vomiting (15/16, 94% each), decreased appetite (10/16, 63%), and abdominal pain, diarrhea and nausea (5/16, 31% each). Grade 3 AEs occurring in 2 or more subjects were anemia, nausea and vomiting (2/16, 13% each). One subject developed DLTs (nausea, vomiting, decreased appetite and fatigue, all Grade 3 at 400 mg BID. The RPTD was determined to be 400 mg BID. Nausea and vomiting were observed at higher incidence than Western and were the major cause of dose modification or discontinuation. PK parameters were dose proportional and comparable to Western. The objective response rate was 14% (2/14 subjects, [95%CI: 1.8% – 42.8%]) with no CR, 2 PR (14%), 6 SD (57%), and 3 PD (21%). Additional CA-125 responder was reported with the longest study duration of 340 days.

Conclusions: V 400 mg BID (RPTD for Western) was considered to be tolerable for Japanese, however, anti-emetic therapy may be needed. Manageable safety profile and no ethnic difference of PK warrant participation of Japan in multinational Phase 3 study.

Clinical trial identification: NCT02210663

Legal entity responsible for the study: AbbVie, Inc.

Funding: AbbVie, Inc.

Disclosure: K. Matsumoto: Institution has received grants from Ono Pharmaceutical, MSD, and AbbVie. K. Tamura: Institution has received grants from Ono Pharmaceutical, MSD, AstaZeneca, Daiichi-Sankyo, Eisai, Pfizer and AbbVie. C. Shimizu: Institution has received grants from Chugai Pharmaceutical, Eli Lilly, and AbbVie. C. Shimizu: Institution has received grants from Chugai Pharmaceutical, Eli Lilly, and AbbVie. K. Yonemori: Institution has received grants from Chugai Pharmaceutical, Eli Lilly, and AbbVie. M. Yunokawa: Has received payment for lectures/speakers from AstraZeneca. H. Higashi: Has received payment for lectures/speakers from AstraZeneca. T. Shimoi: Has received payment for lectures/speakers from AstraZeneca. K. Higashi: Has received payment for lectures/speakers from AstraZeneca. T. Kiyarni: Has received payment for lectures/speakers from AstraZeneca. T. Lebey: Has received payment for lectures/speakers from AstraZeneca. S. Shepherd: Has received payment for lectures/speakers from AstraZeneca. Y. Imaizumi: Has received payment for lectures/speakers from AstraZeneca. K. Tamura: Has received payment for lectures/speakers from AstraZeneca.
Background: Platinum-based chemotherapy is considered standard treatment for platinum-sensitive recurrent ovarian cancer (PSR OC). Real-world data on BRCA mutation (BRCAm) testing, treatment patterns and characteristics of patients (pts) diagnosed with PSR OC is limited and will help to identify unmet medical needs in this population.

Methods: We retrospectively reviewed a random sample of medical records of women having serous PSR OC after 1st-line platinum completion, during 2009-2013. (n=298). Medical records were reviewed to determine if BRCAm testing was performed and if platinum chemotherapy was continued. For patients who discontinued platinum therapy, 2nd-line treatment was documented. Clinical data, including demographics and treatment history, were collected. BRCAm testing was performed on blood samples; when known, direct DNA sequencing was the most commonly used method.

Results: Data from 298 pts were collected in Spain. At diagnosis, median age: 58 years; ECOG 0, 1.38%, 52%, advanced disease stage (21%) 93%, high grade: 80%. Primary tumour sites: ovary (88%), fallopian tube (8%), primary peritoneum (4%). 70% of pts had received prior cytoreductive surgery; 88% received carboplatin + paclitaxel as 1st-line (with or without bevacizumab) (median number of cycles 6) and 4% received intraperitoneal treatment. 7% of pts received maintenance therapy after 1st-line, mainly bevacizumab (5%). The majority of pts (78%) received 2nd-line therapy platinum based 91%, mainly carboplatin + paclitaxel (31%), gemcitabine (15%) or pegylated liposomal doxorubicin (9%). Concomitant bevacizumab. Median times from initial ovarian cancer diagnosis to date of follow up were 20 months. BRCA testing was performed in 83 (28%) of pts and 76 (92%) had a conclusive result available. Of those, 34% were BRCAm. 16% of total pts (69% of BRCAm pts) had family history of BRCA-related cancer (breast 81%; ovarian 41%). BRCA tests were performed on blood (76%) and tumour tissue (24%) samples. BRCA testing method unknown: 65%. When known, direct DNA sequencing was the most used BRCA testing method (16 pts, 55%).

Conclusions: Platinum-based chemotherapy for PSR OC was the standard of care in this review. Bevacizumab was associated with chemotherapy in only 29% of pts. Family history of BRCA related cancer was absent in 31% of BRCAm pts. BRCA testing was not routinely performed. Physicians were mostly unfamiliar with the BRCA testing method used; when known, DNA sequencing was the most commonly used method.

Clinical trial identification: ClinicalTrials.gov NCT01262273 (October 6, 2014)

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Disclosure: N. Colombo I disclose my participation in advisory board by AstraZeneca and corporate-sponsored trials (SOLO1, SOLO2 and ORIO2A). K.L. Davis, J.A. Kaye I am an employee of RTI Health Solutions, which received contract research funding from AstraZeneca for the implementation and conduct of this study and the analyses contained therein. J.R. Robert Lewis, A. Gasco I am an AstraZeneca’s employee. A. Callejo I am an employee of AstraZeneca. All other authors have declared no conflicts of interest.

Quantification of genetic variants as marker of Brca-like phenotype in ovarian cancer

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Background: PARP inhibitors have repeatedly been demonstrated to be active in BRCA mutant ovarian cancers. However, tumors with a BRCA-like phenotype could also benefit from such treatments. Thus, defining molecularly this subtype of ovarian neoplasia has become a priority. We aimed to study the potential role of the quantification of genetic variants in a limited set of genes in this regard.

Methods: We designed a retrospective multi-center study in four collaborating institutions in Spain. Adult patients diagnosed with epithelial ovarian cancer, stage Ic or superior, from 2008 to 2018 were eligible. Clinical data (regarding demographics and treatment outcome) were extracted from medical records by an external data monitor. Whole exome sequencing was performed in extreme cases (best and worst responders) by a panel of five genes highly involved in homologous recombination (BRCA 1 and 2, ATM, CHEK2, RAD51C) was studied through Next Generation Sequencing in middle cases, not previously tested for BRCA mutations. We present the quantitative result of these last patients.

Results: In total 220 patients have been included so far. Discovery cohort accomplish the first 90 cases. Median age was 61 (range 37-87) and tumor stage was I in 10 cases (9%), II in 5 (6%), III in 59 (66%), IV in 13 (14%) and not available in 3 (3%). Tumor histologies were papillary serous (71%), mucinous 1 (1%), endometroid 5 (6%), clear cell (7) (13%), adenosquamous 2 (2%), and non-epithelial 2 (2%). Up to 37 cases have been already analyzed. Median number of genetic variants was 26 (range 12-41). Kaplan-Meier test showed a platinum-free interval of 14.3 months (95% Confidence Interval [CI]: 10.2-18.3) vs 43.3 (95% CI: 11.0-121) for patients with a number of variants below or above the median, respectively.

Conclusions: Though exploratory, our results point to an association between the number of genetic variants in selected genes and a better outcome in advanced ovarian cancer. Mature data of the whole cohort will be presented at the meeting.

Legal entity responsible for the study: Clara Campl Comprehensive Cancer Center Funding: Astra Zeneca Inc. Disclosure: J. Garcia-Donas: Research funding from Astra Zeneca Inc. All other authors have declared no conflicts of interest.

Loss of ARID1A expression is associated with poor prognosis in patients with stage I/II clear cell carcinoma of the ovary


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Background: Clear cell carcinoma of the ovary (CCC) has a poor prognosis because of its resistance to conventional platinum- or taxane-based chemotherapy. Consequently, there is a need to discover biomarkers for predicting the outcome of patients with CCC and develop novel treatment strategies for this disease. Recent studies have shown that somatic mutations in the AT-rich interactive domain 1A (SWI-like) gene (ARID1A) are the most common genetic changes in CCC. This gene is located in chromosome 1p36 and encodes a member of the switch/sucrose-nonfermentable (SWI/SNF) family protein BAF250a (ARID1A). Here, we investigated whether ARID1A could be a prognostic biomarker for this disease.

Methods: Paraffin-embedded specimens were collected from 220 Japanese patients with epithelial ovarian cancer, including 112 CCC and 108 high-grade serous adenocarcinoma of the ovary (HG-SAC). We analyzed the protein expression of ARID1A in these samples by immunohistochemical staining, and evaluated the association of these molecular parameters with clinical outcome.

Results: The loss of ARID1A expression was found in 39.3% (44/112) of CCC, and strong association of these molecular parameters with clinical outcome.

Conclusions: The ARID1A protein may be a promising prognostic marker for FIGO stage I and II CCC. Further studies are needed to clarify the clinical relevance of ARID1A expression in these samples.
Methods: In total, 5,685 EOC and 521 primary peritoneal carcinoma specimens were evaluated (Carus Life Sciences) by immunochemistry (IHC), in situ hybridization (ISH), fusion gene analysis, and next-generation sequencing (NGS). Initial diagnosis was made by the submitting institution and confirmation of diagnosis was made by a pathologist at the centralized laboratory. 

Results: Significant differences were found between IHC and NGS. Protein expression in androgen receptor (28.8% v. 36.5%, p = 0.0011), EGFR (48.9% v. 59.0%, p = 0.0081), ER (46.6% v. 55.6%, p = 0.0001), PD-L1 (19.5% v. 5.7%, p = 0.0300), PR (22.5% v. 14.6% p = 0.0001), TLE3 (18.4% v. 13.2% p = 0.0120), TOP2A (75.9% v. 66.8%, p = 0.0001), and TS (54.3% v. 44.1%, p = 0.0001) varied significantly between IHC and PCC, respectively. Significant differences in mutation rates were found in CTNNB1 (3.3% v. 0.7%, p = 0.0033), KRAS (9.4% v. 3.7%, p = 0.0001), PIK3CA (9.3% v. 4.8%, p = 0.0027), PTEN (3.9% v. 1.6%, p = 0.0222), and TP53 (63.3% v. 74.5%, p = 0.0001). No significant differences were found in amplification rates, as measured by ISH and CNV by NGS.

Conclusions: Multiparametric profiling reveals various potential targets in ovarian and primary peritoneal carcinomas for investigational and drug therapy. Comparison of their genetic profiles reveals two distinct cancers. Dysregulation of the PIK3CA/AKT/mTOR pathway appears to be more common in EOC while loss of TP53 is a more common event in PCC based on this short. More studies are urgently needed to assess differences between EOC and PCC.

Legal entity responsible for the study: N/A

Funding: Carus Life Sciences


Legal entity responsible for the study:

Response to chemotherapy in relapsed low-grade serous ovarian carcinoma: Royal Marsden series of 46 patients

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Background: Low-grade serous carcinoma (LGSC) of the ovary/peritoneum is characterized by slow growth, however there are no reported prospective studies of chemotherapy specifically in this rare subtype. The purpose of this study was to evaluate the response to chemotherapy in patients with relapsed LGSC treated at a single cancer centre.

Methods: A search of a database of patients with histologically confirmed LGSC treated at the Royal Marsden Hospital between 1990-2015 was performed. Patients treated with chemotherapy in the relapsed setting with radiologically evaluable disease were included in the study. Histological confirmation of LGSC was performed by a gynaecology oncologist pathologist. Response was determined by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and confirmed by a radiologist. The primary endpoint was objective response rate (ORR). Secondary endpoints included overall survival (OS) and progression free survival (PFS).

Results: Forty-six patients with relapsed LGSC with evaluable disease, treated with 77 chemotherapy regimens were included in the study. The median age at diagnosis was 49 years (range 22-80 years). There were 8 partial responses with an ORR of 10.4%.

Conclusions: Comprehensive surgical staging was associated with a lower rate of recurrence. Pts with negative prognostic factors perhaps need more aggressive therapy. It requires additional studies for improvement of therapeutic strategy.

Legal entity responsible for the study: N/A

Funding: Budget of clinic

Disclosure: All authors have declared no conflicts of interest.

Phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha (PIK3CA) and microsatellite instability in ovarian clear cell carcinoma, clinical correlation

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Background: Ovarian carcinoma represents a heterogeneous group of diseases. Clear cell carcinoma (CCC), an infrequent subtype, presents particular clinical characteristics and genetic profiles. PIK3CA mutations (PIK3CAmut) in CCC represent the highest frequency among all of the cancer types and a potential treatment target. High microsatellite instability (MSI-H) is known to have a prognostic value in some malignant diseases.

Methods: From a retrospective four-institutional CCC database with cases ranging from 1997 to 2015, 55 ovarian CCCs were analyzed for MSI status and PIK3CAmut and correlated with clinical outcome. A central pathology review was performed. MSI analysis was performed using a conventional PCR method with specific primers for NR27, NR21, NR24 BAT26 and BAT25 mononucleotidic markers and fragment analysis. The PIK3CAmut were detected by real time PCR, using COBAS platform and correlated with clinical outcome. A central pathology review was performed. MSI and PIK3CAmut were evaluated in clinical correlation. A pathological review was performed. MSI analysis was performed using a conventional PCR method with specific primers for NR27, NR21, NR24 BAT26 and BAT25 mononucleotidic markers and fragment analysis. The PIK3CAmut were detected by real time PCR, using COBAS platform and a specific detection kit from Roche (Cobas® PIK3CA Mutation Test).

Results: Fifty-five cases were analyzed for MSI-H and 33 cases for PIK3CAmut in CCC represent the highest frequency among all of the cancer types and a potential treatment target. High microsatellite instability (MSI-H) is known to have a prognostic value in some malignant diseases.

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events. PIK3CAmt had a significant correlation with endometrioid (p = 0.026) and with early stages FIGO I-II (p = 0.04).

Conclusions: In our series, around 25% of CCC had a PIK3CA mt. This mutation was correlated with initial stage disease (I-II) and endometriosis antecedent. Even if MSI-H was infrequent, both molecular events were mutually exclusive. This study was realized with the support of the Jan B. Vermorken Grant from GEICO.

Legal entity responsible for the study: Fundación Instituto Valenciano de Oncología

Funding: Grupo Español de Investigación en Cancer de Ovario

Disclosure: All authors have declared no conflicts of interest.

**884P**

Ovarian granulosa cell tumours: hormone receptor positivity and response to aromatase inhibitors

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**Background:** Ovarian granulosa cell tumours (GCT) are rare gynaecological malignancies with recurrence possible decades after initial treatment. Although mostly treated surgically, often chemotherapy and aromatase inhibitors (AIs) are used with little supporting data. Despite evidence in breast and epithelial ovarian cancer that hormone receptor expression predicts response to AIs, there is no such evidence in GCTs. Oestrogen/progesterone receptor (ER/PR) status poorly reported in case series. Study aim: evaluate clinical efficacy of hormonal manipulation in GCT; correlation of efficacy with immunohistochemical (IHC) marker presence.

**Methods:** Clinical details, demographics, survival data collected. 15 patients with recurrent GCT treated 2004-2014 in UK L centre. ER/PR IHC performed on tumour samples available. Primary outcome: progression free survival on hormonal manipulation (PFS). Secondary outcomes: ER/PR positivity, correlation with response to treatment.

**Results:** Median age at diagnosis 54 years (range 29-79yrs). Median interval from diagnosis to detection of recurrence/advanced disease 5 years (range 0.3-21yrs). Ten patients (67%) received hormonal manipulation, often previously heavily pretreated. Chemotherapy trialed in 4 patients, multiple lines given prior to commencing hormonal manipulation. AI/GnRH prescribed on 14 occasions, sometimes multiple lines in the same patient. Median PFS 14 months (95%CI 11.84-16.95); 5 patients continue to respond at time of analysis. Tumour analysed in 9 instances of hormonal manipulation. ER+ related to longer PFS in those treated with AIs, median 20.5 months (range 9-32); 14 months (range 3-24) in ER- cases.

Table: 884P ER/PR status and progression free survival in episodes of management with hormonal manipulation

<table>
<thead>
<tr>
<th>Hormonal agent</th>
<th>Line of treatment post recurrence</th>
<th>ER/PR (Q score)</th>
<th>Time to radiological progression from commencement of hormonal agent (months)</th>
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<tr>
<td>GnRH</td>
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<td>5/8</td>
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<tr>
<td></td>
<td>2nd</td>
<td>0/8</td>
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<tr>
<td>Letrozole</td>
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* = same patient  
^ = censored data, continues to respond

**Conclusions:** PFS comparable to previous reviews with particularly good response with letrozole. ER+ potentially correlates with prolonged response with AIs, but also PFS comparable to previous reviews with particularly good response with letrozole. ER+ potentially correlates with prolonged response with AIs, but also PFS comparable to previous reviews with particularly good response with AIs, but also PFS comparable to previous reviews with particularly good response with AIs, but also

Legal entity responsible for the study: NHS

Funding: Charitable funding donated to Dr Sarah Williams

Disclosure: All authors have declared no conflicts of interest.

**885P**

Circulating tumor cell number predicts time to progression (TTP) in patients with heavily pretreated gynecological cancers treated with selinexor (SEL)

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**Background:** SEL, an oral, first-in-class selective inhibitor of XPO1-mediated nuclear export (XPO1), induces nuclear retention and activation of tumour suppressor proteins in preclinical models of cervical cancer (CC) & ovarian cancer (OC) and in a phase 1 clinical study. In an effort to identify markers predictive of disease control with SEL, circulating tumour cells (CTCs) were enumerated during the phase 2 trial from patients (pts) with heavily pretreated OC, CC & endometrial cancer (EC). NCT02025985.

**Methods:** Patients with ≥ 2 lines of prior therapy, ECOG PS 0-1, were treated with single agent SEL. At predose C1D1, 7.5 mL of blood was collected in CellSave tubes and CTCs were identified using the Janssen Diagnostics CellSearch System. Intact cells that measured at least 4 microns in size and stained positive for DAPI, EpCAM, and cytokeratin while negative for CD45 were counted as CTCs.

**Results:** CTCs were enumerated at predose C1D1 in 47 (33 OC, 8 EC, 6 CC) of 114 patients. To date, 31 pts had <2 CTCs at predose C1D1 with a median time on study of 108 days while 16 pts had >2 CTCs with a median days on study of 56 days (p = 0.01). Ten patients with >2 CTCs at predose showed stable disease for at least 12 weeks and 4 demonstrated partial response by RECIST 1.1. This study demonstrates that presence of CTCs in pts prior to SEL treatment may correlate with a shorter TTP.

**Conclusions:** Detection of CTC in the peripheral blood of cancer patients has proven feasible and of prognostic value in different neoplasms, including in patients with OC. These results suggest that low CTC count (<2) may also be used to identify pts with heavily pre-treated OC, CC & EC that may benefit from prolonged disease control with single agent oral single agent SEL. Additional studies are planned.

**Clinical trial identification:** NCT02025985

Legal entity responsible for the study: Sharon Shacham

Funding: Karyopharm Therapeutics, Inc.

Background: Lynch Syndrome (LS) is an autosomal dominant disorder caused by germline mutations in any of the mismatch repair genes (MMR: MLH1, MSH2, MSH6 or PMS2). Although colorectal cancer is the most common tumour associated to the syndrome, the risk of endometrial cancer may be higher in some mutation carriers and be diagnosed at an earlier age. Therefore, identifying LS among endometrial cancer patients is crucial to identify LS and also help preventing colorectal cancer as a potential secondary malignancy.

Methods: Patients with endometrial cancer diagnosed less than 60 years of age were prospectively enrolled and their personal and family history was collected. All cases were evaluated for microsatellite instability (MSI), MMR protein expression by immunohistochemistry (IHC) and hypermethylation of the MLH1 promoter (if lack of expression of MLH1 was found). Patients with MSI and/or abnormal immunohistochemical staining were tested for germline mutations by DNA sequencing and large rearrangements analysis, once hypermethylation of the MLH1 promoter was ruled out.

Results: 76 endometrial cancer patients were included, median age was 53 years (range 30-60 years). 27 patients (35%) had molecular findings suggestive of Lynch syndrome and were referred for germline genetic testing. 14 patients (18%) with LS due to a germline mutation in the MMR genes were detected: two patients with a MLH1 mutation, six patients with a MSH2 mutation and six patients with a PMS2 mutation. Despite mutation carriers met classical clinical criteria more frequently than non-carriers (p = 0.001), 29% of mutation carriers did not fulfill them. IHC combined with MLH1 promoter hypermethylation analysis was the most efficient method to select patients for genetic testing with sensitivity of 100%, specificity of 81% and positive predictive value of 54%.

Conclusions: Almost one out five patients with endometrial cancer less than 60 years is carrier of a germline mutation in LS. This justifies referring these patients for genetic counselling and testing. The best screening method to select patients is the combination of IHC with MLH1 promoter hypermethylation for those cases with lack of expression of MLH1.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
Results: Univariate analysis for disease specific survival (DSS) showed, as expected, non-endometrioid histology; grade 3 tumour, presence of lymphovascular invasion (LVI) or myometrial invasion (MI) and advanced International Federation of Gynaecology and Obstetrics (FIGO) stage conferred poor DSS. The overexpression of p53 and pSTMN was also associated with poor DSS. In multivariate analysis grade 3 histology, MI, p53 and pSTMN overexpression were the only factors that remained significantly associated with poor DSS.

Conclusions: For the first time that p53 and pSTMN overexpression are independent predictors of DSS in EC and may be useful prognostic biomarkers. Overexpression of pSTMN may predict sensitivity to PI3K pathway inhibitors in EC. Prospective evaluation is warranted in clinical studies.

Legal entity responsible for the study: UCL Cancer Institute

Funding: UCL Cancer Institute

Disclosure: All authors have declared no conflicts of interest.

Cervical cancer: Awareness and misconceptions of risk factors among lay persons and physicians

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2Medical Oncology, Centre Leon Bérard, Lyon, France, 3Pneumology and Thoracic Oncology, DRC / CHRU of Lille, Lille, France, 4Oncology/Hematological Institutionnal, Roche, Boulogne-Billancourt, France, 5Medical Oncology, Centre Léon Bérard, Lyon, France, 6Oncology, CHRU Bretonneau, Tours, France

Background: Cervical cancer (CC) is the fourth most common cancer in women worldwide. Human papillomavirus (HPV) subtypes 16 and 18 account for 70% of cases of CC. 80% of sexually active French women are infected by HPV at least once in their lifetime. Vaccination and screening are the main weapons against CC. This branch of the EDIFICE survey focuses on awareness of CC risk factors among the lay population and physicians.

Methods: The 4th nationwide observational survey was conducted by phone interviews using the quota method. A representative sample of 737 women (age, 40-75 yrs) was interviewed between June 12 and July 10, 2014. A mirror survey on a representative sample of 105 female physicians was conducted between July 9 and August 8, 2014. Interviewees were asked to cite the five main risk factors for CC.

Results: For 30.3% of lay population participants, heredity/family history was the main CC risk factor while 39.0% of physicians (non-significant difference, NS) ranked it first. For 22.8% of lay persons, sexual practices were cited at very low rates (differences between physicians and lay persons, NS): Tobacco was cited by 23.8% of the lay population (P < 0.01), including multiple partners (70.5% vs. 9.7%, P < 0.01) and unprotected sexual activity (35.2% vs. 9.8%, P < 0.01). Tobacco was cited by 23.8% of physicians and 6.6% of the lay population (P < 0.01). Other known risk factors were cited at very low rates (differences between physicians and lay persons, NS): co-factors such as the pill or multiple pregnancies were cited far less frequently both by physicians and lay persons.

Conclusions: Although not a recognized risk factor for CC, heredity/family history was ranked first by lay persons and second by physicians. Physicians were largely aware of HPV as a major risk factor for CC. They also widely cited notorious risky sexual behavior associated with the risk of contracting HPV, and tobacco, a known cofactor. Lay persons however, were inadequately aware of these risk factors. Other recognized cofactors such as the pill or multiple pregnancies were cited far less frequently both by physicians and lay persons.

Legal entity responsible for the study: Edifice surveys were funded by Roche S.A.

Funding: Edifice surveys were funded by Roche S.A.

Disclosure: X. Pivol, J-F. Monier, S. Couraud, J-Y. Blay, A-B. Cortot, F. Eisinger, L. Grenier: Honorarium fees from Roche. C. Lhomel: Employee of Roche. All other authors have declared no conflicts of interest.

Sexual satisfaction, anxiety, depression and quality of life among Turkish gynecological cancer patients

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Background: Treatments of gynecologic cancer can impact a patient’s self-esteem and body image and can create significant physical barriers, such as pain, to satisfactory sexual experiences, as treatments affect the organs associated with sexuality and in the period of life in which sexuality is of great importance. Gynecological cancer patients (GCPs) suffer from several physical and psychological problems. We aimed to investigate anxiety, depression, quality of life and sexual satisfaction levels of gynecological cancer patients (GCPs).

Methods: In this study, 62 patients with gynecologic cancer were included. The forms consist of GOS, BDI-I, BAI, SF-36 and Hospital Anxiety and Depression Scale (HADS). The chi-square test was used. Statistical analysis was performed with SPSS software.

Results: Statistically significant difference was found in anxiety, depression and quality of life scores and sexual dysfunction. Patients’ quality of life may be increased by taking precautions to reduce their psychosocial and sexual concerns.

Legal entity responsible for the study: Ahmet Alacacoglu

Funding: zorg (Izmır Oncology Group )

Disclosure: All authors have declared no conflicts of interest.
This dosage is often tolerated poorly in the developing world. This study determined the frequency of severe chemotherapy-related toxicity, at a dosage of 30mg/m² in patients receiving radical chemoradiotherapy.

Methods: A retrospective review was performed of patients receiving concurrent chemoradiotherapy for cervical cancer, using weekly Cisplatin, 30mg/m². The frequency of severe chemotherapy-related toxicity (grade 3 and 4) was determined in the following categories: haematologic, renal and upper gastro-intestinal tract toxicity. In order to determine the tolerability of weekly Cisplatin, the number of completed cycles was compared to the intended number, and the average number of cycles completed by each patient was calculated. Age, FIGO stage and HIV status were confounding variables included in the analysis.

Results: The incidence of severe toxicity was low, with renal toxicity (17%) the most common. FIGO stage and HIV status did not influence toxicity significantly. Patients older than 50 years showed a trend for higher toxicity, p-value = 0.094. Approximately three quarter of planned chemotherapy cycles were administered. Sixty-eight per cent of patients received four or five doses of Cisplatin. The remainder received three cycles or less which was deemed inadequate. Reasons for omitted doses were not only toxicity but also included logistical and administrative issues. Outcome data will be presented.

Conclusions: Weekly Cisplatin, 30mg/m², with chemoradiation for cervical cancer is well tolerated. HIV infection did not influence toxicity, but patients over 50 years may have increased risk for adverse events. Stricter adherence to guidelines is recommended.

Legal entity responsible for the study: University of Pretoria, South Africa

Funding: Personal funds

Disclosure: All authors have declared no conflicts of interest.

Comprehensive genomic profiling of uterine carcinosarcomas identifies potential targeted therapy opportunities

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Background: Uterine carcinosarcomas (UCS) are highly aggressive malignancies that are felt to derive from pluripotent malignant cells in Mullerian tract. Studies of primary cancer tissue for stage III, IV or recurrent disease report median OS ranging from 9-15 mos. No effective therapies are available after progression from front line therapy. Comprehensive genomic profiling (CGP) increases the ability to screen for somatic mutations that could direct therapy. This study characterized CGP results for advanced or recurrent UCS disease and compared results to similar analyses for endometrial adenocarcinomas (EA).

Methods: DNA was extracted from FFPE clinical specimens for 100 UCS and 257 EA (including endometrioid and non-endometrioid subtypes). Hybridization captured libraries of 315 genes, plus select introns frequently rearranged in cancer, were sequenced to high median (78%) uniform coverage. All classes of genomic alterations (base substitutions, small indels, rearrangements, and copy number alterations) were evaluated and reported. Clinically relevant genetic alterations (CGRA) were defined as GA associated with on-label targeted therapies and targeted therapies in mechanism-driven clinical trials.

Results: 55% of UCS had at least one clinically relevant alteration (not counting TP53). Mutation frequencies for commonly altered genes are displayed below.

### Table: 894P

<table>
<thead>
<tr>
<th>Gene</th>
<th>UCS</th>
<th>EA</th>
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<tr>
<td>TP53</td>
<td>80%</td>
<td>55%</td>
</tr>
<tr>
<td>PKB3CA</td>
<td>27%</td>
<td>44%</td>
</tr>
<tr>
<td>CCNE1</td>
<td>21%</td>
<td>10%</td>
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<td>PTEN</td>
<td>18%</td>
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<tr>
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</tr>
<tr>
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<td>8%</td>
</tr>
<tr>
<td>FBXW7</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>LYN</td>
<td>14%</td>
<td>3%</td>
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<td>KRAS</td>
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<td>ARID1A</td>
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<tr>
<td>ERRB2</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td>EGFR</td>
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<td>1%</td>
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</tbody>
</table>

Conclusions: Advanced/recurrent UCS are highly malignant neoplasms with poor durable responses to conventional chemotherapy. CGP in this series and others reveals CRGAs also seen in EA, and indicate potential therapeutic sensitivities. More frequent mutation of CCNE1, LYN, and MYC suggest a mechanism for the more aggressive phenotype of UCS. Targeting TP53 GA with WEE-1 inhibitors, KRAS GA with MEK inhibitors, and treating with PARPi when appropriate may benefit patients.

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Foundation Medicine, Inc.

Disclosure: J.A. Elvin, L.M. Gay, S. Ramkisson, S. Ali, I-A. Vergilio, J. Suh, J.S. Ross: Employee of and shareholder in Foundation Medicine, Inc. All other authors have declared no conflicts of interest.

Use of bevacizumab (Bev) in real life for first-line (II) treatment of ovarian cancer (OC), Part 1: the ENCOURAGE cohort of 1158 patients (pts) by GINECO


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Background: Bev has obtained European (EU) approval for EOC pts treated in II on 12/2011. This study addresses the question of how Bev is used in routine practice for the II treatment of OC pts.

Methods: 102 centers were selected to be representative of the distribution of OC pts in France. All consecutive OC pts treated in II in each center were screened in order to include at least 500 pts who gave their consent to participate to the ENCOURAGE cohort evaluating the long term Bev use in routine practice. We report here how Bev was prescribed in this series of pts.

Results: From 04/2013 to 02/2015, 1158 evaluable pts representing 15% of French cohort evaluating the long term Bev use in routine practice. We report here how Bev was prescribed in this series of pts.

Conclusions: Advanced/recurrent UCS are highly malignant neoplasms with poor durable responses to conventional chemotherapy. CGP in this series and others reveals CRGAs also seen in EA, and indicate potential therapeutic sensitivities. More frequent mutation of CCNE1, LYN, and MYC suggest a mechanism for the more aggressive phenotype of UCS. Targeting TP53 GA with WEE-1 inhibitors, KRAS GA with MEK inhibitors, and treating with PARPi when appropriate may benefit patients.

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Foundation Medicine, Inc.

Disclosure: J.A. Elvin, L.M. Gay, S. Ramkisson, S. Ali, I-A. Vergilio, J. Suh, J.S. Ross: Employee of and shareholder in Foundation Medicine, Inc. All other authors have declared no conflicts of interest.
Overexpression of HER2/neu in uterine carcinosarcoma
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Background: Uterine carcinosarcoma (UCS) is a rare tumor in gynecologic malignancy, comprising less than 5% of uterine cancers, and is known to be clinically highly aggressive. UCS is often excluded from the eligibility of clinical trials, because of its rarity and poor prognosis. For recurrent or metastatic UCS, combination therapy of ifosfamide and paclitaxel is recommended as first line chemotherapy, and combination therapy of carboplatin and paclitaxel is also useful. However, the efficacy of existing chemotherapy for UCS is relatively limited and the research of molecular targeted therapy for UCS is behind in development because of its property. The main aim of this study is to evaluate HER2/neu expression status in UCS.

Methods: After approval by the internal review board, we retrospectively evaluate HER2/neu expression status in UCS, using the archives with formalin-fixed paraffin-embedded tissue blocks of UCS from patients. All patients were treated in National Cancer Center Hospital, Tokyo, Japan from 1998 to 2016, and the expression of HER2/neu in UCS was examined by immunohistochemistry (IHC). The current results suggest that molecular therapy targeted HER2 has a potential to be a new treatment for UCS.

Legal entity responsible for the study: National Cancer Center Hospital, Tokyo, Japan

Funding: National Cancer Center Hospital, Tokyo, Japan

Disclosure: All authors have declared no conflicts of interest.

Comprehensive genomic profiling of uterine leiomyosarcomas identifies opportunities for personalized therapies
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Background: Uterine leiomyosarcoma (uLMS) respond poorly to conventional chemotherapeutic agents, and personalized therapies have not yet been systematically explored. We hypothesize that comprehensive genomic profiling (CGP) of uLMS will identify therapeutic targets and provide insight into the biology of this highly aggressive tumor.

Methods: CGP of 232 FFPE uLMS and 138 male LMS clinical specimens by hybridization-capture of up to 405 cancer-related genes provided genomic alterations (GA) which were compared between uLMS and LMS.

Results: Analysis of clinically advanced/recurrent uLMS from women with a median age of 69 years (range 23-76 years) revealed that 96.5% harbor at least one GA (mean 3.5; range 0-40). Mutations frequencies in uLMS were compared to those in a cohort of 138 LMS cases from 1998 to 2016, and the expression of HER2/neu in UCS was examined by immunohistochemistry (IHC). The current results suggest that molecular therapy targeted HER2 has a potential to be a new treatment for UCS.

Conclusions: Her2/neu expression was identified in half of patients with UCS, and we must verify the significance of HER2 2+ in UCS by in situ hybridization (ISH). The current results suggest that molecular therapy targeted HER2 has a potential to be a new treatment for UCS.

Legal entity responsible for the study: National Cancer Center Hospital, Tokyo, Japan

Funding: National Cancer Center Hospital, Tokyo, Japan

Disclosure: All authors have declared no conflicts of interest.

Defining the genomic landscape of vulvar squamous cell carcinoma (VSCC) using next generation sequencing: the role of HPV infection
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Background: Vulvar squamous cell carcinoma (VSCC) is associated with physical and psychological morbidity. Targeted therapies have not influenced outcomes, in part because the genomic landscape of VSCC remains incompletely understood and is complicated by two etiologies: HPV-dependent and HPV-independent disease. Next-generation sequencing (NGS) was used to identify somatic mutations by HPV status (+/-).

Methods: We conducted a retrospective review of patients (pts) seen at the Ottawa Hospital, Ottawa, Canada between 2008-2012 for VSCC. Clinical and pathological data was collected and pts with adequate tumor for HPV and molecular analysis were identified. HPV status was determined by polymerase chain reaction (PCR) with
primes targeting the L1 region of HPV DNA. The Ion AmpliSeq™ Cancer Hotspot Panel v2 is being used to examine the presence of 50 known mutations.

**Results:** Forty-seven pts with VSCC were included. 22/47 (47%) were HPV− and 25/47 (53%) were HPV+. Median age at diagnosis was 60 years (IQR 49.76) and 69 years (IQR 58.77), for HPV+ vs HPV−, respectively. Disease stage by IGR status (v+ - v-) was: I (15 vs 16), II (2 vs 0), III (2 vs 9) and IV (3 vs 0). Molecular data is available on 31 pts (17 HPV+ vs 14 HPV−). Among HPV+ pts, 15/17 had ≥ 1 mutation. Mutational frequencies among HPV+ pts were: TP53 7/17, PIK3CA 6/17, KDR 3/17, KIT: 3/17, FGFR3 3/17, and one mutation each of PTEN, CNTPN1, ACP, KRAS, ERBB4, ATM, SMARCB1, FLT3, CDK2A. Among the HPV− pts, 12/14 had ≥ 1 mutation. Mutational frequencies among HPV− pts were: TP53 8/14, HRAS 3/14, CDK2A 2/14, PIK3CA 2/14, KDR 1/14 and GNA11 1/14.

**Conclusions:** VSCC is characterized by a high mutation rate and a high prevalence of HPV infection. HPV− dependent and HPV− independent disease have unique mutational profiles. The high prevalence of “actionable” mutations supports the need for trials of targeted therapies. Molecular data on the full study cohort (n = 47) will be presented.

**Legal entity responsible for the study:** N/A

**Funding:** University of Ottawa Pathology and Laboratory Medicine (PALM) Enrichment Fund

**Disclosure:** G. Goss: Previously received honoraria and consulting fees from AstraZeneca, Roche, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb and Pfizer and research monies from AstraZeneca. All other authors have declared no conflicts of interest.

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**901T1P KEYNOTE-100: Phase 2 trial of pembrolizumab in patients with advanced recurrent ovarian cancer**

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**Background:** Ovarian cancer is the most lethal gynecologic cancer, with approximately 86% of patients experiencing disease recurrence following standard front-line therapy. Currently, no curative therapy is available for recurrent ovarian cancer (ROC), which is an area with high unmet medical need. Pembrolizumab is a programmed death 1 (PD-1) inhibitor designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. Prior study of pembrolizumab in advanced epithelial ovarian cancer showed promising clinical activity. Here, we further evaluate the efficacy and safety of pembrolizumab in patients (pts) with advanced ROC in the open-label, single-arm, 2-cohort KEYNOTE-100 study (NCT02674061).

**Trial design:** Pts who are ≥18 years old with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and confirmed disease recurrence following front-line platinum-based therapy can be enrolled. Cohort A will include approximately 250 pts who received ≤2 prior therapies for ROC and had a platinum-free interval (PFI) or treatment-free interval (TFI) of ≥3 to 12 mo based on the last regimen received. Cohort B will include approximately 75 pts who received ≥3 prior therapies for ROC and had a PFI or TFI of ≥3 mo based on the last regimen received. Pts must also have measurable disease and ECOG performance status of 0-1 at baseline and must provide a tumor sample for PD-L1 analysis. Pts will be treated with pembrolizumab 200 mg every 3 wk for 35 cycles or until disease progression, death, unacceptable toxicity, or withdrawal of consent. Pts will have regular imaging and safety assessments during the study. The primary study objectives are to evaluate objective response rate per RECIST v1.1 (primary end point) in cohort A and cohort B all-comer populations and in tumor PD-L1 high expression populations. Duration of response, progression-free survival, overall survival, and safety will also be evaluated.

**Clinical trial identification:** NCT02674061

**Legal entity responsible for the study:** Merck & Co., Inc.

**Funding:** Merck & Co., Inc.

**Disclosure:** All authors have declared no conflicts of interest.

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**901T1P Phase Ib/II study to evaluate the efficacy and tolerability of PM01183 (turbinecibtedin) in combination with olaparib in patients with advanced solid tumors**

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1Oncogen Department, Fundación Instituto Valenciano de Oncología, Valencia, Spain, 2Vall d’Hebron University Hospital Institut d’Oncologia, Barcelona, Spain, 3Medical Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, 4Medical Oncology, Vall d’Hebron University Hospital Institut d’Oncologia, Barcelona, Spain, 5Clinical Research, Pharmamar, Madrid, Spain, 6Data Center, Fundación Instituto Valenciano de Oncología, Valencia, Spain, 7Laboratory of Molecular Biology, Fundación Instituto Valenciano de Oncología, Valencia, Spain

**Background:** PM01183 is a new anticancer drug that exerts antitumor activity through inhibition of trans-activated transcription and modulation of tumor microenvironment. Recently a significant activity in platinum-resistant ovarian cancer patients in terms of Response Rates (RR), has been reported (Poveda A et al. ASCO 2014 abstr #5503). PM01183 is currently being studied in different solid tumors. Olaparib (AZD2281, KU-0059436) is a potent Poly(ADP-ribose) polymerase (PARP) inhibitor (PARP-1, -2, -3) with proven antitumor activity in homologous recombination deficient (HRD) tumors. Olaparib is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents. The combination of PM01183 and Olaparib has shown synergistic activity in cell-lines independent of HRD status.

**Trial design:** This first-in-human phase I-II study evaluates the safety and tolerability of PM01183 in combination with short course of Olaparib through a 3 × 3 dose escalation design Selection of patients: Phase-I patients with advanced or metastatic solid tumors without established standard therapeutic alternatives. Phase-II expansion cohort: platinum-resistant ovarian cancer patients (epithelial non-mucinous), triple negative breast and endometrial cancer patients. For patients included in the phase-II part of the study, evidence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will be required. Primary endpoints are Phase-I safety (MTD, DLT and RP2D), Phase-II: overall response rate. Secondary endpoints: Progression Free survival, Overall survival, PK and pharmacodynamic profiles, safety profile. Additional translational research to analyze predictive factors to further select potential patients to be explored in the phase-II part of the study have been recruited at the end of April 2016 (enrollment started Nov 2015).

**Clinical trial identification:** NCT02684318

**Legal entity responsible for the study:** N/A

**Funding:** Pharmamar, AstraZeneca

**Disclosure:** A.M. Poveda, Roche, AstraZeneca, Pharmamar, Clovis Advisor. A. Oaknin Roche, AstraZeneca, Clovis Advisor. A. Soto: Pharmamar employee and market share owner. All other authors have declared no conflicts of interest.

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**901T1P ENDOLA : A GINECO-GINEGEPS French NCI sponsored phase I/II trial to assess the safety and efficacy of metronomic cyclophosphamide, metformin and OLAPARIB in recurrent advanced/metastatic ENDometrial cancer patients**


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**Background:** Beyond first line treatment with platinum-based chemotherapy, there is lack of effective and well tolerated regimens for patients with metastatic endometrial carcinomas (EC). The combination of metronomic cyclophosphamide + metformin + olaparib may be effective because ECs are characterized by frequent alterations in the PI3K, IGF1R and DNA repair pathways. In addition, IGF1R signaling promotes effective DNA repair via homologous recombination (HR) and PI3K inhibition induces HR deficiency. Metronomic cyclophosphamide may be synergistic with olaparib via both its alkylating and anti-angiogenic effects, with a favorable toxicity profile. Finally, metformin may increase the anti-proliferative effects of olaparib because it suppresses IGF1R and PARP-1 and Inot, for negative breast and endometrial cancer patients. For patients included in the phase-II part of the study, evidence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will be required. Primary endpoints are Phase-I safety (MTD, DLT and RP2D), Phase-II: overall response rate. Secondary endpoints: Progression Free survival, Overall survival, PK and pharmacodynamic profiles, safety profile. Additional translational research to analyze predictive factors to further select potential patients to be explored in the phase-II part of the study have been recruited at the end of April 2016 (enrollment started Nov 2015).

**Clinical trial identification:** NCT02755844

**Legal entity responsible for the study:** Benoit You

**Funding:** Institut National du Cancer, Astra Zeneca, ARCAGY-GINECO

**Disclosure:** All authors have declared no conflicts of interest.
Properative olaparib in early-stage endometrial cancer (EC): A phase 0, window of opportunity trial to evaluate the PARP inhibition effect, targeting cell cycle-related proteins (PLODEN study)


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Background: Olaparib (AZD2281, KU-0059436) is a poly ADP ribose polymerase (PARP) inhibitor. Previous studies have shown relevant clinical activity as single agent in ovarian, breast and prostate cancers with BRCA1/2 mutations. However, little is known about the activity of PARP inhibitors in EC. The aim of this study is to identify pharmacodynamic and pharmacogenetic biomarkers associated with a short term exposure to olaparib in type I primary EC patients (pts).

Trial design: Phase 0, multicenter, single arm, window of opportunity trial in women with type I primary EC candidate to surgery. They receive a 28 days course of olaparib tablets, 300 mg twice daily before surgery. The study was approved by the IRB from 5 participating sites in Spain. Major eligibility criteria are (1) pts aged ≥18 years with histologically confirmed type I primary EC, (2) who have not received prior anticancer therapies for current disease and (3) adequate organ function and performance status. The trial uses an exact single stage design. The primary endpoints are the significant inhibition rate above which the treatment warrants further exploration is 35%; the variation among the baseline values in all the sample. These pts are considered to have a 95% confidence that it is not due to chance compared to the variation among the baseline values in all the sample. These pts are considered responders. The inhibition rate below which the treatment is considered inactive is 5%. The inhibition rate above which the treatment warrants further exploration is 35% with type I and II errors of 5%, the sample size is 36 pts with 36 responders as threshold. The secondary objectives include the measurement of the correlation between PARP inhibition and mitosis, angiogenesis and apoptosis in tumor-tissue samples. Among secondary objectives is to estimate the potential predictive role of PTEN loss in clinical tumor changes and PARP inhibition. Four women have been recruited for the trial since study start on March 2016. The expected end of accrual will be on November 2016.

Clinical trial identification: NCT02506816, EudraCT 2015-001156-30

Legal entity responsible for the study: Medical Sciences Innovation, MedSIR-ARO

Funding: Astra Zeneca

Disclosure: I. Romero: advisory board. Astra Zeneca, Roche Speaker’s bureau. Astra Zeneca, Roche, Pharmamar. A. Llobríbart-Cussac: has received honoraria lectures and advisory boards from Roche, GlaxoSmithKline, Novartis, Celgene, Eisai and AstraZeneca and research funding from GlaxoSmithKline, Sanofi and Fuma Biotechnology. All other authors have declared no conflicts of interest.

Interim statistical analysis on a phase III randomised trial investigating the addition of modulated electo-hyperthermia to chemoradiation for cervical cancer in HIV positive and negative women in South Africa

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Background: Cervical cancer is the second most common cancer in South Africa where funding and resources for treatment are limited and HIV infection rates are high. A Cochrane review (2010) on pooled data from six randomised trials showed a potential benefit to the addition of hyperthermia (HT) to chemotherapy (CT) protocols for cervical cancer. The Dutch Deep Hyperthermia trial (2010) reported a cost saving per quality adjusted life year when HT was added to CT protocols. The potential cost-saving resulting from the addition of HT to cervical cancer treatment protocols may lower the burden on healthcare facilities in South Africa and improve treatment options in HIV positive patients.

Trial design: The aim is to determine the clinical effects of the addition of modulated electo-hyperthermia (mEHT) on the standard treatment protocols for locally advanced cervical cancer patients in state healthcare in South Africa. The objectives are to assess the effects of the addition of mEHT on local disease control, quality of life, acute and late toxicity and survival. Method: This is an ongoing phase III randomised clinical trial conducted at the Charlotte Maxeke Johannesburg Academic Hospital. The study aims to enroll 236 female participants with FIGO stage IIIb (distal parametrium involvement) to IIIB cervical cancer (no bilateral pelvic lymphadenopathy). Participants are being randomised into a “Hyperthermia” group (mEHT plus chemoradiation) and a “Control” group (chemoradiation alone), based on HIV status, age and stage of disease. All participants are receiving 25 fractions of 2Gy external beam radiation, 3 doses of high dose rate brachytherapy (68Gy) and up to 3 doses of cisplatin (80mg/m²). The Hyperthermia group is receiving two 55 minute local mEHT treatments per week during radiation therapy. Local disease control is being assessed by 18-24 month follow-up. The Hyperthermia group may lower the burden on healthcare facilities in South Africa and improve treatment options in HIV positive patients.

Clinical trial identification: South African Department of Health Trial Registration number: DOH-27-0113-4012, Issued 26 June 2012

Legal entity responsible for the study: University of the Witwatersrand

Funding: National Research Foundation: Technology and Human Resources for Industry Programme (THRIP); Thembisa Labs; C-Therm Africa (pty) Ltd

Disclosure: C.A. Minnaar: Shareholder in C-Therm Africa (pty) Ltd, and has been employed by the company at the university as a PhD candidate, on a National Research Foundation Grant. All other authors have declared no conflicts of interest.

METRO-BIBF Phase II, randomised, placebo controlled, multicentre, feasibility study of low dose (metronomic) cyclophosphamide (MCy) with and without nintedanib in advanced ovarian cancer (AOC)

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Background: AOC patients have generally been heavily pretreated with intravenous (IV) chemotherapy (CT) and their prospects are limited – median overall survival (OS) of 9 mo. MCy is an oral option which is well tolerated, does not require IV access or numerous hospital visits and has clinical benefit lasting >4 months for 19-25% (Kummar 2015, Hall 2010). MCy has anti-angiogenic properties; it has been shown to inhibit endothelial cells in tumour and host vasculature. Augmenting this mechanism has been explored in AOC by the addition of bevacizumab to MCy where ORR of ≥30% have been reported for high grade serous AOC (PS-6.2mo and median OS 16.9 mo) (Chura 2007, Garcia 2008). Nintedanib (N) is an oral tyrosine kinase inhibitor (TKI) which inhibits VEGFR, PDGFR and FGFR. Combining MCy with N offers an oral option to control symptoms in patients with AOC maintaining QoL with minimal toxicity. This trial of MCy +/- N: will explore the activity of MCy alone and the potential benefits of adding N.

Trial design: A placebo controlled, randomised phase II design, with direct comparison of OS, aiming to detect an increase of 2 mo, i.e. median OS in the combination arm of 7 mo (HR 0.71). Patients with AOC who have received 2 or more lines of chemotherapy for AOC, are platinum resistant / intolerant and/or not suitable for any further IV CT, with ECOG PS 0-2 and life expectancy of ≥6 weeks will be recruited. All receive MCy 100mg/day continuously with N placebo at 200mg bd until progression. The starting dose was later reduced to N 150mg bd due to a perceived excess of TKI related toxicity (abdominal cramps and diarrhoea).

Patients will be stratified for prior treatment with bevacizumab but previous anti-angiogenic TKI is NOT preclusion. The potential benefits of adding N include safety, ORR only for patients with evaluable disease at trial entry, PFS and QoL. 89 of 124 patients have been recruited to date.


Legal entity responsible for the study: University College London

Funding: Boehringer Ingelheim

Disclosure: All authors have declared no conflicts of interest.
haematological malignancies

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Phase 3 randomised study of daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR


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Background: Daratumumab (D), a human CD38 lgG4 monoclonal antibody, induces deep and durable responses with a favorable safety profile in RRMM pts. We report a pre-specified interim analysis of the first randomised, controlled study of D (CASTOR, NCT02126134).

Methods: Pts with ≥1 prior line of therapy were randomised (1:1) to 8 cycles q3w of DVd/Vd (V: 1.3 mg/m2 sc on Days 1, 4, 8, 11; d: 20 mg po Days 1, 2, 4, 5, 8, 9, 11, 12) ± D (16 mg/kg iv qe in Cycles 1-3, 1 Day of Cycles 4-8, then qtw until progression). Primary endpoint was PFS.

Results: 498 pts (DVd, 251; Vd, 247) were randomised. Baseline demographics and disease characteristics were well balanced. Pts received a median of 2 prior lines of therapy (range 1-10). 76% received prior IMiD; 66% received prior V; 48% received prior PI and IMiD; 33% were IMiD-refractory; 32% were refractory to last line of prior therapy. With a median follow-up of 7.4 months, D significantly improved PFS (61% reduction in risk of progression), ORR, rates of VGPR, rates of CR and delayed time to next therapy (Table). Median OS was NR in both groups. Most common (≥25%) AEs (DVd/Vd) were thrombocytopenia (59%/44%), peripheral sensory neuropathy (47%/38%), diarrhea (32%/23%) and anemia (29%/31%). Most common grade 3/4 AEs (>10%) were thrombocytopenia (45%/33%), anemia (14%/16%), neutropenia (13%/4%). 7% of pts discontinued due to a TEAE. D-associated infusion-related reactions (45% of pts) mostly occurred during the first infusion, most were grade 1/2 (grade 3/4, 9%/0%). Additional subgroup analyses will be presented.

Conclusions: D in combination with Vd significantly improved PFS and ORR and delayed time to next therapy vs Vd alone. D doubled both VGPR and CR/PR rates vs Vd alone. Safety of D/Vd is consistent with the known safety profile of D and Vd. The addition of D to Vd should be considered as a new standard of care for RRMM pts currently receiving Vd alone.

Clinical trial identification: NCT02126134

Legal entity responsible for the study: N/A

Funding: Janssen Research & Development, LLC

Disclosure: K. Weisel: Honoraria from BMS, Celgene, Amgen, Onyx, Janssen, Novartis, Takeda; Consulting / Advisory role for BMS, Celgene, Amgen, Onyx, Janssen, Novartis, Takeda, Research Funding (for my institution) from Celgene and Janssen and A. Palumbo: Honoraria from Janssen; Consulting / Advisory role for Novartis; Research Funding (for my institution) from Janssen. A. Charman-Khan: Research Funding (for my institution) for clinical research; A.K. Nooka: Consulting or advisory role for Novartis, Amgen, Spectrum Pharm. I. Spica: Honoraria from Celgene, Janssen, Amgen; Consulting or advisory role for Celgene, Janssen, Amgen, RMS. T. Massi: Comedex or advisory role for Takeda; BMS, Janssen-Cilag, M. Bekác: Honoraria from Janssen-Cilag, Celgene, Amgen, Novartis; BMS, Speaker’s Bureau for Janssen-Cilag, Celgene, Amgen, RMS; V. Hungria: Consulting or advisory role for Janssen, Takeda, M. Munder: Consulting or advisory role for Janssen, Amgen, Teva; Takeda; Travel, Accommodations, Expenses from Janssen, Takeda, BMS. M.-V. Mateos: Honoraria from Janssen, Celgene, Amgen, BMS, Takeda; Consulting or advisory role for Janssen; V. Yang: Consulting or advisory role for Janssen, Celgene, Takeda; A. Spencer: Honoraria from Janssen-Cilag, Consulting or advisory role for Janssen-Cilag, Speakers Bureau for Janssen-Cilag, Research Funding from Janssen-Cilag-M. Qi: Employment with Johnson & Johnson, Stock or other ownership in Johnson & Johnson & T. J. Schecter: Employment with Janssen; Stock or other ownership from Janssen; H. Amin: Employment with Janssen Research & Development, LLC; Stock or other ownership from Johnson & Johnson, Merck, others via mutual funds. X. Qin: Employment with Janssen R&D. W. Deraedt: Employment with Johnson & Johnson; Stock or other ownership with Johnson & Johnson & T. Ahmadi: Employment with Janssen Research & Development; Stock or other ownership with Johnson & Johnson & P. Sonneveld: Honoraria from Amgen, Janssen, Celgene, Takeda; Consulting or advisory role for Amgen, Janssen, Celgene, Takeda; Research Funding (for my institution) from Amgen, Janssen, Celgene, Karyopharm.

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Safety and efficacy of clarithromycin monotherapy in patients (pts) with extranodal marginal zone lymphoma (EMZL)

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Background: Evidence revealing anticancer effects of macrolides is growing. Clarithromycin, the most studied one, is safe and active in pts with EMZL (Govi et al. BJH 2010; Ferreri et al. Ann Oncol 2015), but the best administration schedule and dose remain to be defined. We analyzed a retrospective series of 55 pts with EMZL treated with three different regimens of clarithromycin monotherapy, at two institutions, between 2005 and 2015, to establish the best regimen for future trials.

Methods: Clarithromycin regimens were: 500 mg x 2/d, every day, for 6 months (n = 13), 3 cycles of 500 mg x 2/d, days 1-21, q 35 (n = 19), and 4 cycles of 2 g/d, days 1-14, q 21 (n = 23).

Results: Median age was 65 (range 30-88), with a M:F ratio of 0.57. EMZL affected a single organ in 40 pts, and was multifocal in 15: the main involved organs were ocular adnexae (n = 30), stomach (n = 9) and lung (n = 7). PIF score was 0.1 in 40 pts and 2-4 in 15; the IELSG risk score (age, LDH and stage) was 0 in 25 pts, 1 in 23 and >1 in 7. A prior history of HBV/HCV, H. pylori and C. psittaci were recorded in 20 pts; 5 pts had multiple infections. Clarithromycin was the 1st line in 8 pts, the 2nd or more in 7. Tolerability was excellent: the main side effects were grade 1-2 nausea (17), dysgeusia (7), dizziness (4), and headache (3); only 2 pts had grade-3 toxicity (nausea). 5 pts interrupted treatment due to nausea (3), rash or dysgeusia. Nausea was more common in the 2-g/d regimen (52% vs. 25%, p = 0.05). Response was complete in 13 (24%) pts and partial in 13, with an overall response rate (ORR) of 47% (95% CI = 34-60). ORR was higher (78% vs. 41%, p = 0.04). At a median follow-up of 33 months (range 7-137), 29 pts remain progression-free, with a 3-year PFS of 52 ± 7%; refractory disease and IPI ≥2 were independent predictors of poor

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Background: CNS dissemination is lethal in DLBCL. However, risk predictors and effective prophylaxis remain to be defined. Thus, we analysed the value of a risk-tailored CNS prophylaxis in a mono-institutional retrospective series of 242 pts with DLBCL in the rituximab era.

Methods: Consecutive HIV-negative pts with DLBCL treated with first-line R-CHOP or similar 7 R were considered. CNS dissemination risk was based on involvement of specific extranodal organs (lungs, kidney/adenal, spine, skull, paranasal sinuses, orbit, and/or breast) and/or International Prognostic Index (IPI) of 4-5. CNS prophylaxis, consisting of 3-4 cycles of MTX 3 g/m² ± intrathecal chemotherapy (IT) was indicated in pts with high CNS recurrence risk diagnosed after 2007.

Results: 242 pts were analysed (median age 66, range 18-89). CNS dissemination risk was low in 147 (61%) and high in 95 (39%). Prophylaxis was indicated in 47 high-risk pts: 36 pts received HD-MTX at IT. 11 pts received only IT due to MTHFR polymorphism, comorbidity or old age. Unexpected toxicity and intercurrents were not recorded. At a median follow-up of 51 months (12-171), 11 (4.5%) pts experienced CNS relapse: 6 in the parenchyma, the others in the meninges. CNS relapse rate was <1% (1/147) in low-risk pts and 11% (10/95) in high-risk pts. 8 of these pts died of CNS progressive disease after 7-37 months (median 12). In the high-risk subgroup, CNS relapse rate was 17% (8/48) in pts who did not receive CNS prophylaxis, 18% (2/11) in pts who received IT alone and 0% (0/36) in pts who received HD-MTX ≥ IT (p = 0.048). Overall, 38 high-risk pts experienced relapse, and CNS was the most common involved site (n = 10). The addition of HD-MTX significantly improved PFS (3-yr: 81% vs. 46% p = 0.001) and OS (3-yr: 86% vs. 48% p = 0.00005) independently from IPI score and extranodal sites.

Conclusions: HD-MTX-based prophylaxis is highly effective in DLBCL with increased risk of CNS recurrence defined by involvement of certain extranodal organs and/or high IPI score. The relevant OS effect of HD-MTX can be explained by the high-mortality associated with CNS relapse; however, an influence on systemic disease control cannot be excluded.

Legal entity responsible for the study: IRCCS San Raffaele Scientific Institute, Milan, Italy.

Funding: IRCCS San Raffaele Scientific Institute, Milan, Italy.

Disclosure: All authors have declared no conflicts of interest.
months (39.75 interquartile range). 108 patients received curative intent treatment, chemotherapy (CT) alone in 26%, radiation and CT (CTXRT) in 74%. Median radiation dose was 38 Gy (range 30-60 Gy), 96/108 received 6-8 cycles of chemotherapy. At the end of planned treatment, 82.5% were in complete remission (CR), 13.8% showed partial response and only 4 patients had primary progressive disease. Systemic relapse or progression was observed in 22%, with no local recurrence. 5-year overall survival (OS), and progression free survival (PFS) were 82.5% and 76.2% respectively. Disease status at last follow-up was 77% patients were alive and in CR, 2% alive with disease, 16% died of disease and 5% died of another cause or lost to follow up. 28 patients progressed or relapsed, 6 received high dose CT and autologous bone marrow transplant (all are alive and in CR) and 19 died of disease. In univariate analyses (log rank test), favorable prognostic factors for PFS were low or low intermediate International Prognostic Index (IPI) score (P = 0.06), CTXRT (P = 0.033), and no B symptoms (P = 0.081). For OS, low or low intermediate IPI score (P = 0.007), stage I-II disease (P = 0.03), CTXRT (P = 0.005), and no B symptoms (P = 0.01) were favorable. Multivariate analysis showed low or low intermediate IPI score, CTXRT and no B symptoms independently influencing PFS. Absence of B symptoms was the only predictor for OS.

Conclusions: This is largest data from the Middle East. PBL has good prognosis. Local control is excellent, and systemic failure occurs infrequently. Good IPI score (<2), CTXRT and absence of B symptoms were positive prognostic factors. The role of combine chemotherapy and radiotherapy is central in the treatment of PBL and seems to overcome the bad prognostic feature of bulky disease.

Legal entity responsible for the study: Institutional review board of King Faisal Hospital and Research Center.

Funding: Institutional review board of King Faisal Hospital and Research Center.

Disclosure: All authors have declared no conflicts of interest.

Prevalence, clinico-pathological features and outcomes of ‘double-hit’ high-grade B-cell non-Hodgkins lymphoma (NHL): a single institution experience

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Background: MYC/BCL2 (or MYC/BCL6) double hit lymphoma (DHL) is defined as a large B-cell lymphoma with concurrent translocations. Several studies indicate that up to 10% of diffuse large B-cell lymphomas (DLBCLs) harbouring a MYC rearrangement will have a poorer prognosis, worse still when present with a BCL2/6 rearrangement. Currently, there is a paucity of guidelines bridging together this data to decide the most effective therapy for DHL patients.

Methods: From August 2013 to October 2015, all patients with high grade B-cell NHL who had tissue samples referred to the central pathology laboratory at St James Hospital, Dublin were included for analysis. Patient demographics, clinical features, histopathological details, systemic therapy received and patient-related outcomes were recorded from electronic or paper medical records. All cases were reviewed by a consultant haematopathologist.

Results: 152 cases of high grade B-cell NHL were identified since FISH testing for MYC re-arrangement commenced in St James Hospital. In 21 patients displayed DHL, 9 of whom had a concurrent BCL2 rearrangement. One patient with MYC and BCL2 rearrangements also had a BCL6 rearrangement. These patients all had germinal centre cell of origin (GC COO) by Hans criteria. 4 patients with DHL had prior follicular lymphoma and 5 patients had no prior lymphoma. Patients were treated with varying regimens including standard or dose-intensified chemo-immunotherapy. All patients with DHL achieving a complete response (CR) were consolidated with transplantation (n = 5), both in first line and salvage settings. 2 patients underwent autologous transplantation and 3 underwent allogeneic transplantation. The 1-year survival for all DHL patients was 67%

Conclusions: In our study of all high-grade NHL, the frequency of DHL was 6%. All patients had GC COO by Hans criteria. We suggest considering referral of all patients with DLBCL for MYC-rearrangement testing at the time of initial diagnosis with consideration given to upfront dose-intensified chemotherapy and early haematogenous cell transplantation referral, once DHL status is known.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Impact of the addition of rituximab in overall survival in first line chemotherapy in follicular lymphoma: a population-based study from the Spanish Lymphoma Oncology Group (GOTEL)

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Background: The optimal treatment of follicular lymphoma (FL) is not well established. There is no doubt that the clinical development of rituximab (R) has been a significant breakthrough in FL. However, its effect on overall survival (OS) in these patients is still open to debate. Methods: We reviewed 1076 patients treated in our country diagnosed with FL. They were included in the Follicular Lymphoma Registry, a prospective registry within GOTELs (Spanish Lymphoma Study Group) database that includes all new lymphoma cases, regardless of their histological subtype, diagnosed in the hospitals within the Group between January 1st 1999, and January 1st 2009. Data were obtained from 16 sites. The median follow up was 54.9 months (0.13-663.12) for the entire series.

Results: The addition of R to the chemotherapy regimen was significantly associated with a superior OS (P < 0.001), compared to treatment without R. The multivariate analysis in our series shows that there were significant factors of poor prognosis in the R group which were age > 60 years of age (p = 0.033); ECOG > 1 (p = 0.002); Stage III-IV (p = 0.004); more nodal and extranodal involvement (p < 0.003); > LDH

Disclosure: All authors have declared no conflicts of interest.

Prognosis of diffuse large B-cell lymphoma: 16 years of experience

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Background: Diffuse large B-cell lymphoma (DLBCL) accounts for the majority of cases of non-Hodgkin’s lymphoma in our country. However, little is known about its clinical and demographic data and prognosis. The aim of this study is to summarize the demographics and to investigate the prognosis of DLBCL patients from a tertiary reference hospital in Turkey over the past 16 years.

Methods: This study was designed as a retrospective cohort study. Patient who were diagnosed and/or treated at the University of Hacettepe between 1/2000 and 11/2015 were included. A chart review was conducted to access the clinical and demographic data. Main outcome measures (overall survival (OS), survival after progression (time from relapse to second progression or death, SAP)) were calculated. The role of combine chemotherapy and radiotherapy is central in the treatment of PBL and seems to overcome the bad prognostic feature of bulky disease.

Results: A total of 939 cases were included. Mean age of patients was 54 ± 17; 54% of the patients were male and 43.8% were female. Ann Arbor stages at presentation were as follows: stage 1 in 15.8% of patients, stage 2 in 23.4%, stage 3 in 21.1% and 39.7% as stage 4. It is of note that extranodal involvement was present (64.6%). The most prevalent extranodal sites were gastrointestinal system (17.3%), central nervous system (4.4%), bone (4.4%), skin (2.4%) and Iver (2%). Mean overall survival was 94 ± 12.3 months. At 5 years, 93.2% of patients were alive and at 10 years 85.2% of patients were alive. There was a statistically significant survival difference between stage III and IV patients (p < 0.001), whereas mean OS had not yet been reached for stage I and II patients. Patients without any extranodal involvement lived significantly longer than patients with EN involvement (p = 0.001) and presence of bone marrow involvement was found to be statistically significant for OS (p < 0.001).

Conclusions: Extrapolation is present in more common in DLBCLs in Turkey and clinical parameters such as stage, EN status and BM involvement are the main prognostic factors.

Legal entity responsible for the study: N/A

Funding: Authors

Disclosure: All authors have declared no conflicts of interest.
Follicular lymphoma is the second most common tumor of lymphoid origin. Despite a generally favorable prognosis, the disease presents a median survival of approximately 10 years and is considered incurable. Many treatments have been incorporated into this disease, and according to the FLIPI, the benefits were the greatest in follicular lymphoma (FL) compared with those expected in the general population. For this reason, R is associated with better overall survival, especially in patients treated with chemoradiotherapy, while there were no significant differences between patients treated with chemotherapy and chemoradiotherapy. In the late stages group, 5-year OS was 64% in patients treated with chemotherapy vs. 78% in patients treated with chemoradiotherapy, p = 0.24. In the early stages group, 5-year OS was 77% in patients treated with chemotherapy vs. 84% in patients treated with chemoradiotherapy, p = 0.24. In the late stages group, 5-year OS was 64% in patients treated with chemotherapy vs. 78% in patients treated with chemoradiotherapy, p = 0.26. The difference in OS rates was revealed only between the groups of chemoradiotherapy and vs. without rituximab (p = 0.026) and chemotherapy with rituximab vs. chemoradiotherapy with rituximab (p = 0.01). In the early stages group, 5-year OS was 77% in patients treated with chemotherapy vs. 84% in patients treated with chemoradiotherapy, p = 0.24. In the late stages group, 5-year OS was 64% in patients treated with chemotherapy vs. 78% in patients treated with chemoradiotherapy, p = 0.26. Survival in young adults diagnosed with follicular lymphoma in a national registry from the Spanish Lymphoma Oncology Group

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Background: Follicular lymphoma is the second most common tumor of lymphoid origin. In Spain, between 3,000 and 5,000 new cases of follicular lymphoma are diagnosed each year. The cut-off age in the prognostic evaluation of patients is 60 years of age. A recently published study compared the clinico-pathological characteristics of 155 patients diagnosed with follicular lymphoma before 40 years of age with older patients in a series of 1,002 cases in 4 European centers over a 25-year period between 1985 and 2010.

Methods: The Spanish Lymphoma Oncology Group analyzed the survival and clinicopathological characteristics of patients registered in our national database of 1178 FL patients recruited between 1986 and 2012, and who were diagnosed prior to 40 years of age. A survival analysis was made using SPSS v19.

Results: The median age at diagnosis was 58 years, similar to the 56 years of age reported previously. The median survival in our series was 234 months, almost 20 years (95% CI 212-255), while the series reported in the recent article referred to was only 12.5 years. Similarly, we observed longer survival in those who were younger than 40 years at diagnosis, who have not yet reached the median survival, and a median of 16.3 years in patients older than 40 years, with these differences being statistically significant (P < 0.0001). In our series, in patients younger than 40 years of age, we also observed a greater incidence of elevated beta2-microglobulin, less high-risk FLIPI and a lower rate of increased LDH, with the latter at the limit of statistical significance (P = 0.062). However, the differences found with respect to bone marrow involvement, involvement of more than 4 lymph nodes or the presence of bulky mass (>7cm) at diagnosis were not statistically significant. Nevertheless, we did find differences in performance status (PS) with a higher percentage of ECOG ≥ 1 in FL patients younger than 40 years of age (P = 0.000).

Conclusions: We believe that 40 should be the cut-off age in the prognostic evaluation of patients with follicular lymphoma rather than the classic 60 years of age.

Legal entity responsible for the study: Spanish Lymphoma Oncology Group

Funding: Spanish Lymphoma Oncology Group

Disclosure: All authors have declared no conflicts of interest.
A pooled data analysis of 12 clinical trials of Fondazione Italiana Linfomi (FIL): Khorana score and histotype predict the incidence of early venous thromboembolism (VTE) in non-Hodgkin lymphoma (NHL)

Background: VTE in NHL occurs in most cases within 3 months from diagnosis and can have substantial impact on treatment delivery and outcome. However, few data are available on potential predictors. We conducted a pooled data analysis of 12 clinical trials from FIL. Our analysis included basic demographic features, lymphoma-related characteristics as well as the Khorana score (based on histology, BMI, platelets WBC and HB counts) which is extensively used in solid tumors to predict VTE risk.

Methods: From Jan. 2010 to Dec. 2014, all pts with B-cell NHL enrolled in prospective clinical trials from FIL for frontline treatment were included. The analyses were conducted based on CRFs as well as pharmacovigilance reports. Cumulative incidence of VTE from the study enrollment was estimated using the method described by Gooley et al. accounting for death from any causes as a competing event. The Fine & Gray survival model was used to evaluate predictors of VTE among NHL pts. Factors predicting the grade of VTE were investigated using an ordinal logistic regression model.

Results: Overall, 177 patients belonging to 12 studies were evaluated. M/F ratio was 1.41, median age was 57. Histologies were: DLCL-B 34%, FL 41%, MCL 18%, other 6%. Median BMI was 25. Median Hb, WBC and platelets counts were: 13 g/dl, 7.1 x 10^9/l, 1.41, respectively. Overall 59 any grade VTE episodes occurred in 51 pts (2.9%). Usage of ibrutinib and idelalisib grew from 0% in 2012 to 66% in 2015, bendamustine/rituximab 17P/TP53 has remained stable with an average of 15%; among which, usage of ibrutinib or idelalisib containing regimens increased from 0% in 2012 to 30% in 2015, bendamustine/rituximab remained stable at around 37% and FCR (fludarabine/cyclophosphamide/rituximab) decreased from 18% to 7%.

Conclusions: Over 2/3 of all CLL patients in EUS are now tested for 17P/TP53, which coincides with the increase in ibrutinib and idelalisib usage in 17P/TP53 positive patients and 17P/TP53 negative patients in 2nd line. Although bendamustine/rituximab still holds the lead among 17P/TP53 negative 2nd line patients, it is likely that ibrutinib and idelalisib based regimens will continue to take patient share in the coming year. The launch of venetoclax, indicated for the same population, could have an impact on the positive trend we have observed for these two molecules.

Legal entity responsible for the study: IMS Health

Funding: IMS Health

Disclosure: All authors have declared no conflicts of interest.

VEGFR, VEGFR2 and GSTM1 polymorphisms in outcome of multiple myeloma patients in the thalidomide era

Background: Angiogenesis (AG) abnormalities are crucial in pathogenesis of multiple myeloma (MM), and give support to treat patients with angiogenic agents. However, patients with similar clinicopathological aspects may present distinct outcome under AG inhibitors treatment. Single nucleotide polymorphisms (SNPs) in genes involved in blood vessels formation may constitute a plausible explanation for this finding. This study aimed to investigate the roles of VEGF c.-2595C > A (rs699947), c.-1154G > A (rs1570360), c.-634G > C (rs2010963), c.*237C > T (rs3025039), VEGFR2 c.-906T > C (rs2071559) and c.889G > A (rs2059948) SNPs, and GSTM1 and GSTT1 genes in outcome of MM patients treated with thalidomide-based regimens.

Methods: The study comprised 102 MM patients diagnosed between June 2005 and June 2013. The tumor was diagnosed and staged by standard criteria. Therapeutic regimens consisted in thalidomide combined with steroids and chemotherapy, followed or not by autologous stem cell transplantation. Response was evaluated at the end of therapy using the International Myeloma Working Group guidelines. Genotypes were analyzed in genomic DNA by polymerase chain reaction based methods. The chi-square test and logistic regression model were used to identify variables influencing response to therapy. Survival was estimated by Kaplan-Meier method, log-rank test and Cox hazards models.

Results: Patients with the wild-type allele of VEGF c.-2595C > A alone or plus the wild-type allele of VEGFR2 c.-906T > C SNPs, and the CGGC haplotype of all respective VEGF SNPs had 3.55, 9.91, and 3.86 more chances of achieving better response to therapy than others. At 60 months of follow-up, patients with VEGFR2 c.889G > A, VEGFR2 c.889G > A plus VEGFR2 c.889G > A, and VEGFR2 c.889G > A plus GSTM1 present genotypes had 2.62, 2.64, and 2.80 more chances of presenting disease relapse or progression, and 2.21, 4.88, and 4.23 more chances of evoking to death in multivariate analysis, respectively.

Conclusions: Our data present, for the first time, a preliminary evidence that VEGF c.-2595C > A, c.-1154G > A, c.-634G > C, c.*237C > T, VEGFR2 c.-906T > C and c.889G > A SNPs, and GSTM1 gene after outcome of MM patients under thalidomide therapy.

Legal entity responsible for the study: University of Campinas

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

17P deletion and TP53 gene mutation (17P/TP53) testing behaviour and treatment patterns for chronic lymphocytic leukaemia (CLL) patients in France, Germany, Italy, Spain and UK (EUS)

Background: CLL patients with 17P/TP53 frequently progress earlier to symptomatic disease and have shorter response durations with traditional chemoimmunotherapy. In 2013, two new targeted therapies, brutinib and idelalisib, were introduced into the CLL market. Both are indicated for patients tested positive for either 17P/TP53, or patients who have received at least one previous treatment. The objective of this study is to demonstrate the progression in 17P/TP53 testing in EUS since 2012, and to evaluate how treatment choices have evolved in carriers of these chromosomal abnormalities.

Methods:IMS Oncology Advantage CLL, an anonymised patient database collected retrospectively through quarterly physician panel survey has been used, looking at 4 years of data from 2012 to 2015 for EU5 countries.

Results: Out of 2800, 2693, 2657 and 2983 patients diagnosed in 2012, 2013, 2014 and 2015 respectively, 17P/TP53 testing was performed in 48% (2012) to 78% (2015) of patients in all lines of therapy. Within the tested population, the level of positivity for 17P/TP53 has remained stable with an average of 15%, among which, usage of brutinib and idelalisib grew from 0% in 2012 to 66% in 2015, bendamustine/rituximab combination therapy decreased from 18% to 10% and alentuxumab monotherapy from 27% to 2%. Negativity for 17P/TP53 among 214 Line patients remained stable with an average of 88%, among which usage of brutinib or idelalisib containing regimens increased from 0% in 2012 to 30% in 2015, bendamustine/rituximab remained stable at around 37% and FCR (fludarabine/cyclophosphamide/rituximab) decreased from 18% to 7%.

Conclusions: Over 2/3 of all CLL patients in EUS are now tested for 17P/TP53, which coincides with the increase in brutinib and idelalisib usage in 17P/TP53 positive patients and 17P/TP53 negative patients in 2nd line. Although bendamustine/rituximab still holds the lead among 17P/TP53 negative 2nd line patients, it is likely that brutinib and idelalisib based regimens will continue to take patient share in the coming year. The launch of venetoclax, indicated for the same population, could have an impact on the positive trend we have observed for these two molecules.

Legal entity responsible for the study: IMS Health

Funding: IMS Health

Disclosure: All authors have declared no conflicts of interest.

Targeted immune therapy based on PD-1/PD-1L suppression has revolutionized the treatment of various solid tumors. A remarkable improvement has also been observed in the treatment of patients with refractory/refractory classical Hodgkin lymphoma (cHL). We investigated PD-L1 status in a variety of treatment resistant lymphomas.
The predictive value of immunohistochemical expression of Bcl-2, Bcl-6, MUM1, CD10 and CD30 in patients with diffuse large cell lymphoma

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Background: Diffuse large B-cell lymphoma (DLBCL) is a potentially curable disease, but the first line of therapy is not effective for 40% of patients, and new markers for prognosis are needed. Immunohistochemistry (IHC) markers commonly used for lymphomas diagnosing may have predictive significance. There are some publications regarding predictive and prognostic roles of IHC expression of Bcl-2, Bcl-6, MUM1, CD10 and CD30, but their controversial results are at issue.

Methods: The retrospective analysis of IHC expression of Bcl-2, Bcl-6, MUM1, CD10 and CD30 in 267 DLBCL patients was done. Patients were treated at the National Cancer Institute since 2011 and received rituximab-based chemotherapy.

Results: There was positive expression of Bcl-2 in 84% of patients, positive expression of Bcl-6 in 63%, positive expression of MUM1 in 62%, positive expression of CD10 in 39% and positive CD30 expression was determined in 26% of patients with DLBCL. There were not significant differences in the positive expression of such markers as Bcl-2, MUM1 and CD30 between groups “R” and the “PR” (84.7% vs 82.1%, 60.2% vs 66.7%, 23.3% vs 25.0%, p > 0.05, respectively). There was a trend toward more frequent positive expression of CD10 in the “R” group 44.3% vs 28.6%, p < 0.05. The positive expression of Bcl-6 was significantly more common in the “R” group in comparison with a “PR” group (69.9% vs 58.1%, p < 0.05). There was no difference in gender, age, the number of high risk patients, patients with advanced disease and patients who received immunotherapy between compared groups.

Conclusions: Positive expression of Bcl-6 is significantly more common in patients who responded to first line treatment. It may indicate the predictive value of this biomarker for identifying the group of patients who respond to the first line therapy.

Legal entity responsible for the study: N/A

Funding: National Cancer Institute

Disclosure: All authors have declared no conflicts of interest.
Readers variability of PET/CT-based response criteria in DLBCL and association to outcome

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Background: F-18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is essentially recommended for monitoring response to treatment in patients with diffuse large B cell lymphoma (DLBCL) and quantitative interpretation is commonly applied in clinical practice. We aimed to evaluate interobserver agreements of qualitative PET/CT-based response criteria and evaluate predictive value of PET/CT results by each reader for outcome.

Methods: FDG PET/CT images were obtained for patients with DLBCL at baseline, at interim after 3 cycles of first-line chemotherapy and after completion of chemotherapy. Two nuclear medicine physicians (with 3 and 8 years of experience with FDG PET/CT) blinded to clinical data retrospectively assessed response to chemotherapy using visual qualitative analyses from the International Working Group (IWG) criteria and Lugano classification, respectively. The associations between PET/CT results and progression-free survival (PFS) and overall survival (OS) were assessed using Cox regression analysis.

Results: Included were 112 PET/CT images from 59 patients with DLBCL (36 male, 23 female, mean age 53 ± 14 years). In interpretation using binary scoring system from IWG criteria, interobserver agreement was substantial (Cohen’s κ = 0.76) with absolute agreement consistency of 89%. In interpretation using Deauville five-point scale from Lugano classification, interobserver agreement was moderate (Cohen’s weighted κ = 0.54) and absolute consistency was 62%. The most common cause of disagreements was discordant interpretation of presence of residual tumor uptake. With mean follow-up period of 88 months, estimated 3-year PFS and OS were 81% and 92%, respectively. Neither interim nor post-treatment PET/CT results by both readers were significantly associated with PFS. Interim PET/CT result using Deauville scale was the only significant factor for OS.

Conclusions: Moderate to substantial interobserver agreement was observed for response assessment according to visual analysis and interim PET/CT result could predict OS in patients with DLBCL. Further studies are necessary to validate completely PET/CT-based response criteria and further standardize and consistent PET/CT interpretation.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Chemotherapy-induced interstitial pneumonia in patients with lymphoma

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Methods: Between 2009 and 2014, 2212 consecutive patients with newly diagnosed lymphoma were enrolled as subjects. IP was defined as diffuse pulmonary interstitial infiltrates found on computed tomography scans. IP was observed in 108 patients. Of these, 23 were excluded from the study: 6 due to infection, 7 due to clinical trials with new drugs, 8 due to onset during salvage chemotherapy for recurrent-relapsed lymphoma, 2 due to incomplete medical records. Finally, 85 patients with IP were included in this study. The clinical features, laboratory results, and histological types were analyzed. Patients were paired according to age, sex and pathological type. Risk factors of IP were investigated with matched pair analysis.

Results: The incidence of IP was 3.9% (7/178) in non-Hodgkin lymphoma and 2.4% (7/315) in non-Hodgkin lymphoma (P = 0.210). The median number of chemotherapy courses before IP was 3 cycles. The median time from the cessation of chemotherapy to...
IP was 17 days. All patients were administered with glucocorticoids, but 11 (13.3%) developed respiratory failure, and 3 (3.6%) died from a progression of pneumonia. Sixty-six (79.5%) patients experienced chemotherapy delays, and 14 (16.9%) had premature termination of their chemotherapy. Sixty-nine patients were re-treated with chemotherapy after remission of IP, of which 22 (31.9%) experienced IP recurrence. The incidence of IP recurrence was significantly higher in patients re-treated with previous regimen than those with alternative regimen (65.4% vs. 11.6%, P < 0.001). In a multivariate Cox regression model, B symptom (HR = 4.221, P < 0.001) and history of drug allergy (HR = 4.019, P = 0.011) were identified as risk factors of IP.

**Conclusions:** IP is a rare but life-threatening complication in lymphoma patients. Therapy with glucocorticoids may be a favorable strategy for IP. However, IP may recur in patients re-treated with chemotherapy, especially when previous regimen is re-administered.

**Legal entity responsible for the study:** Peking University Cancer Hospital

**Funding:** National Natural Science Foundation of China (Grant No. 81241073)

**Disclosure:** All authors have declared no conflicts of interest.

### Pharmacokinetics (PK) and safety of carfilzomib (CFZ) in patients (Pts) with advanced malignancies and varying degrees of hepatic impairment (HI): an open-label, single-arm, phase 1 study


**Background:** A phase I study evaluated PK and safety of CFZ in Pts with relapsed or progressive advanced malignancies.

**Methods:** Adult Pts with normal (Norm) hepatic function (fcn) or, mild, moderate (Mod), severe (Sev) HI received CFZ infusions on 4 consecutive days (D) each week (wk) for 3 wks (D 1, 2, 8, 9, 15, and 16) in 28-D cycles (C); 20 mg/m² on D1-D2 of C1; escalated to 27 mg/m² on D8 of C1; if tolerated, 56 mg/m² started on D1 of C2. PK parameters were evaluated using a non-compartmental approach. The CFZ PK in HI Pts was compared with Norm Pts using summary statistics and analysis of variance (ANOVA) of In-transformed PK parameters.

**Results:** 11 Pts; 17 Mild, 14 Mod, 4 Severe Pts enrolled; 61% male, mean age 62 years. Following CFZ 27 and 56 mg/m², an overlapping exposure was observed between groups. There was an inconsistent trend for increased area under the curve (AUC) and maximum serum concentration (Cmax) in mild/Mod HI Pts (table). Median duration of exposure was 6 (Norm), 4.3 (Mild), 2.3 (Mod), and 0.8 (Severe) wks. No severe HI Pts were PK-evaluable. Thirty-five (76%) Pts had grade ≥ 3 adverse events (AEs) including 15 Pts with treatment-related grade ≥ 3 AEs. Grade ≥ 3 increased blood bilirubin (22%, Mod HI Pts only), anemia (15%), fatigue (15%), and increased alanine aminotransferase (9%, Mod HI Pts only) occurred in ≥ 3 Pts.

**Conclusions:** No marked differences in exposures (AUC and Cmax) were observed between Norm Pts and mild/Mod HI Pts following the CFZ dose. No consistent trend in CFZ exposure related to HI severity was seen. HI did not appear to substantially increase severity of AEs; however, the number of Pts was small. Based on PK and limited safety results, no CFZ dose adjustment appears to be warranted in Pts with relapsed or progressive advanced malignancies and mild or Mod HI.

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>27 mg/m²</th>
<th>56 mg/m²</th>
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<tbody>
<tr>
<td>Norm (n = 8)</td>
<td>Mild HI (n = 14)</td>
<td>Mod HI (n = 9)</td>
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<tr>
<td>AUC(0–5)</td>
<td>378</td>
<td>546</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>392</td>
<td>351</td>
</tr>
<tr>
<td>Geometric C.V.</td>
<td>144 (113.1, 126.1)</td>
<td>-</td>
</tr>
<tr>
<td>Geometric mean, % (90% CI)</td>
<td>107.3</td>
<td>183</td>
</tr>
<tr>
<td>Geometric CV, %</td>
<td>144 (113.1, 126.1)</td>
<td>-</td>
</tr>
<tr>
<td>Geometric mean, % (90% CI)</td>
<td>107.3</td>
<td>183</td>
</tr>
<tr>
<td>AUC(0–-last)</td>
<td>348</td>
<td>529</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>457</td>
<td>364</td>
</tr>
<tr>
<td>Geometric C.V.</td>
<td>151 (133.6, 161.5)</td>
<td>183.3</td>
</tr>
<tr>
<td>Geometric mean, % (90% CI)</td>
<td>151 (133.6, 161.5)</td>
<td>183.3</td>
</tr>
</tbody>
</table>

* n = 8; n ≥ 12; n ≥ 7; n = 6; CV coefficient of variation

**Disclosure:** All authors have declared no conflicts of interest.

**Funding:** National Cancer Institute (Grant No. CA054184), National Institute of Diabetes and Digestive and Kidney Diseases (NC 01319256), National Heart, Lung, and Blood Institute (HL112493), National Institute on Drug Abuse (DA035854), National Institute of Mental Health (MH116701, MH087619, MH108107), National Institute of General Medical Sciences (GM103505), National Institute of Allergy and Infectious Diseases (AI112722, AI112724), Department of Defense (W81XWH-16-2-0003, W81XWH-16-1-0032, W81XWH-16-1-0033), California Department of Public Health (1MB-0121), The UCSF Cancer Center Support Grant (P30CA33572), the UCSF Helen Diller Family Foundation, and the UCSF-MIIT Cancer Center (P30CA008748), the Parker Institute for Cancer Immunotherapy.

**Disclosure:** All authors have declared no conflicts of interest.

**Legal entity responsible for the study:** University of California at San Francisco

**Funding:** UCSF Helen Diller Family Foundation, The UCSF Cancer Center Support Grant (P30CA33572), the UCSF-MIIT Cancer Center (P30CA008748), the Parker Institute for Cancer Immunotherapy.

**Disclosure:** All authors have declared no conflicts of interest.
Final results of a phase II trial of R-IDEA as salvage therapy in patients with relapsed/refractory diffuse large B-cell lymphoma

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Disclosure: All authors have declared no conflicts of interest.

Methods: This study includes pts aged 18-65 years with primary refractory or first relapse CD20+ DLBCL after R-CHOP. The R-IDEA regimen consists of R 37.5mg/m2 on day 1, IFO 2.5g/m2, ETP 75mg/m2 on days 2-4, Dec 33mg IV on days 2-5 and Ara-C 750mg/m2 twice daily on days 3-4. R-IDEA was administered every 21 days for a total of 3 cycles. Pts were excluded after cycle 3. SDH regimen was based on institutional preference. Primary endpoint was mobilization adjusted response rate (MARR; CR + PR - mobilization failure). Secondary endpoints included 2-year overall survival (OS), 2-year progression-free survival (PFS), transplanted rate, mobilization efficiency and toxicity.

Results: 101 patients were enrolled (median age 59.5, range 42-65, M:F ratio 11:9). 17 pts were enrolled after first relapse and three were refractory to first line chemotherapy. Five pts relapsed within 1 year of diagnosis. The most frequent grade 3/4 adverse events were neutropenia, thrombocytopenia, anemia, and febrile neutropenia as a result of completion of R-IDEA chemotherapy, seven pts achieved CR, five PR, one had SD, seven had PD. The median CD34+ cell count was 2.6 million/kg (0.17-43.7) and median number of apheresis days was two. In 12 sensitive relapsed pts, two failed to mobilization, for a MARR of 50% (10/20). No patient of primary refractory or relapsed within 1 year after diagnosis achieved MARR. In total, 12 (10 pts with MARR, 1 pt in SD and 1 pt in CR with CD34+ 1.5 million/kg) received HDT/ASCT. The OS and PFS at two years was 38.6% and 28.2%, respectively.

Conclusions: As previously reported in PARMA study and CORAL study, primary refractory and early relapsed DLBCL pts had an extremely poor prognosis. New treatment strategies seems to be warranted for the high risk pts.

Clinical trial identification: UMIN000004892 (release date: 20 Jan, 2011)

Legal entity responsible for the study: The society of lymphoma treatment in Japan

Funding: The society of lymphoma treatment in Japan (Sot-L-T) and the west japan hematology/oncology group (WestJHOG)

Disclosure: All authors have declared no conflicts of interest.
Methods: Gonadal function, its regulation by tropic pituitary hormones and levels of prolactin and cortisol were studied by radioimmunoassay in 32 HL patients aged 12–21 years receiving chemotherapy.

Results: Before therapy females showed estradiol decreased by 10 times compared with the norm in follicular and luteal phases of the cycle, with testosterone increased by 3.5 times in phase I and by 10 times in phase II of the cycle. Follicle-stimulating hormone (FSH) was 10 times lower than the norm. Lateormizing hormone in the luteal phase was similar to the norm in all disease stages, and in the follicular phase it was decreased by 15 times in patients with stage III-II disease, compared with the norm. Male patients, especially those with stage III-I disease, showed low testosterone levels in the blood before treatment. Significant overproduction of estradiol was observed, especially in stages III-IV. FSH levels in stage III-II patients were 11 times lower than the norm; cortisol content did not change in stages I-II, and in stages III-IV it was 2.5 times higher than the norm. Prolactin and progesterone levels were similar to the norm.

Conclusions: HL development in adolescents is accompanied by significant changes in levels of sex and pituitary hormones and cortisol depending on the disease stage. Chemotherapy provides high antimutator effect and normalizes the levels of circulating hormones that have changed before the treatment.

Legal entity responsible for the study: Boston Research Institute of Oncology

Funding: Ministry of Health of the Russian Federation

Disclosure: All authors have declared no conflicts of interest.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>Patients with cytogenetic relapse (n = 52)</th>
<th>Patients without cytogenetic relapse (n = 52)</th>
<th>P value</th>
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<tbody>
<tr>
<td>CYP3A5-A989G</td>
<td>AA</td>
<td>8 (35%)</td>
<td>6 (43%)</td>
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</tr>
<tr>
<td></td>
<td>AG</td>
<td>23 (55%)</td>
<td>19 (45%)</td>
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<tr>
<td>MDR1-C1236T</td>
<td>GG</td>
<td>21 (44%)</td>
<td>27 (56%)</td>
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<td></td>
<td>CT</td>
<td>34 (50%)</td>
<td>34 (50%)</td>
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<tr>
<td>MDR1-C3435T</td>
<td>TT</td>
<td>7 (13%)</td>
<td>15 (29%)</td>
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<tr>
<td></td>
<td>CT</td>
<td>28 (55%)</td>
<td>21 (43%)</td>
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<td>GG</td>
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<td>16 (30%)</td>
<td>19 (37%)</td>
<td>0.069</td>
</tr>
<tr>
<td>CYP3A5-A6986G</td>
<td>AA</td>
<td>8 (57%)</td>
<td>6 (43%)</td>
<td>0.492</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>23 (35%)</td>
<td>19 (45%)</td>
<td></td>
</tr>
<tr>
<td>CYP3A5-C516T</td>
<td>CC</td>
<td>11 (79%)</td>
<td>3 (21%)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>34 (50%)</td>
<td>34 (50%)</td>
<td></td>
</tr>
<tr>
<td>CYP3A5-T751G</td>
<td>CT</td>
<td>28 (57%)</td>
<td>21 (43%)</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>34 (63%)</td>
<td>24 (46%)</td>
<td></td>
</tr>
<tr>
<td>G695A</td>
<td>GA</td>
<td>2 (8%)</td>
<td>1 (3%)</td>
<td>0.335</td>
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</tbody>
</table>

Trough levels of Imatinib (ng/mL) 1551.4 ± 1324.1 2154.2 ± 1358.3 0.041

Conclusions: C1236T & C3435T genetic polymorphisms in MDR1 gene significantly influence the risk of cytogenetic relapse in patients with CML. Genotyping of MDR1 gene may be considered in patients with CML to individualize the therapy & optimize the outcomes.

Legal entity responsible for the study: All India Institute of Medical Sciences, New Delhi

Funding: All India Institute of Medical Sciences, New Delhi (Institute funding)

Disclosure: All authors have declared no conflicts of interest.

Relationship between adherence, drug level and clinical response achieved in patients with chronic myeloid leukemia on imatinib therapy

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Background: Imatinib mesylate (IM) has been shown to be highly efficacious in the treatment of chronic myeloid leukemia (CML). Continuous and adequate dosing is essential for optimal outcomes so patient adherence is critical. There is a considerable

| Table: 936P Frequency of genotypes and trough levels of imatinib in patients with and without cytogenetic relapse |
|----------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| SNP | Genotype | Patients with cytogenetic relapse (n = 52) | Patients without cytogenetic relapse (n = 52) | P value |
| CYP3A5-A989G | AA | 8 (35%) | 6 (43%) | 0.492 |
| | AG | 23 (35%) | 19 (45%) | |
| MDR1-C1236T | GG | 21 (44%) | 27 (56%) | 0.024 |
| | CT | 34 (50%) | 34 (50%) | |
| MDR1-C3435T | TT | 7 (13%) | 15 (29%) | 0.010 |
| | CT | 28 (55%) | 21 (43%) | |
| MDR1-G2677TA | GG | 7 (13%) | 3 (6%) | 0.453 |
| | GT | 23 (44%) | 21 (42%) | |
| MDR1-3435T | TT | 16 (30%) | 19 (37%) | 0.069 |
| CYP3A5-A6986G | AA | 8 (57%) | 6 (43%) | 0.492 |
| | AG | 23 (35%) | 19 (45%) | |
| CYP3A5-C516T | CC | 11 (79%) | 3 (21%) | 0.024 |
| | CT | 34 (50%) | 34 (50%) | |
| CYP3A5-T751G | CT | 28 (57%) | 21 (43%) | 0.010 |
| | TT | 34 (63%) | 24 (46%) | |
| G695A | GA | 2 (8%) | 1 (3%) | 0.335 |

Trough levels of Imatinib (ng/mL) 1551.4 ± 1324.1 2154.2 ± 1358.3 0.041

Conclusions: C1236T & C3435T genetic polymorphisms in MDR1 gene significantly influence the risk of cytogenetic relapse in patients with CML. Genotyping of MDR1 gene may be considered in patients with CML to individualize the therapy & optimize the outcomes.

Legal entity responsible for the study: All India Institute of Medical Sciences, New Delhi

Funding: All India Institute of Medical Sciences, New Delhi (Institute funding)

Disclosure: All authors have declared no conflicts of interest.

Do MDR1 & CYP3A5 genetic polymorphisms influence the risk of cytogenetic relapse in patients with chronic myeloid leukemia on imatinib therapy

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Background: Genetic polymorphisms in the genes coding for imatinib transporters & metabolizing enzymes might be responsible for marked inter-individual pharmacokinetic variability seen with imatinib. Whether these polymorphisms influence the risk of cytogenetic relapse in patients with CML on imatinib therapy is unknown.

Methods: Patients with chronic phase CML on imatinib therapy & have completed 5 years of follow-up were enrolled. The following single nucleotide polymorphisms were genotyped: C1236T, C3435T, G2677T & G2677A in MDR1 gene and A989G in CYP3A5 gene. Genotyping was done using PCR-RFLP method & validated by direct gene sequencing. Plasma trough levels of imatinib were measured using LC-MS/MS.

Cytogenetic relapse was defined as the presence of Philadelphia chromosome positive metaphases in conventional bone marrow cytogenetic study in patients who had already achieved complete cytogenetic response.

Results: A total of 104 chronic phase CML patients (52 cases with cytogenetic relapse & 52 controls without cytogenetic relapse) were included. Mean age at diagnosis was 36 years. Among the SNPs genotyped, statistically significant difference in the frequency of various genotypes was seen for MDR1-C1236T & C3435T polymorphisms, between the patients with & without relapse (table 1). Patients with CC genotype for MDR1-C1236T polymorphism had a statistically higher risk of relapse (OR = 4.382, 95%CI (1.145, 16.774), p = 0.022), while those with TT genotype for MDR1-C3435T polymorphism had a significantly lower risk of relapse (OR = 0.309, 95%CI (0.134, 0.708), p = 0.005). Patients with relapse had lower trough levels of imatinib compared to those without relapse (table).
variability in the level of molecular responses achieved with IM therapy. These differences could result from variable drug levels which may be due to adherence factor or other factors. This study was designed to determine the relation between drug adherence, ini mutant plasma level and clinical response.

Methods: This study was designed as a prospective, observational, non-interventional study. A total of 101 patients with chronic-phase CML treated with IM were enrolled. The study protocol was approved by the Institutional Review Board of the National Cancer Institute of Cairo University, Egypt. Adherence was monitored by using Morisky medication adherence scores (MMAS). Drug level was measured as peak and trough concentration after reaching steady state using high performance liquid chromatography mass spectroscopy (HPLC/MS) and peak/trough ratio (P/T ratio) was calculated.

Results: The mean IM trough plasma level in patients who achieved unfavorable response (n = 37) was 1183.92 ng/ml, and in patients who achieved favorable response (n = 64) 1560.16 ng/ml (p = 0.006). The P/T ratio in patients who achieved unfavorable response was 3.03 and in patients who achieved favorable response 2.06 (p = 0.001). There was no significant correlation between adherence score and clinical response. Multivariate analysis identified P/T ratio as the only independent predictors of clinical response.

Conclusions: In patients with CML treated with IM the significant independent factor affecting response was P/T ratio. As the peak/trough ratio increase by one, the risk of poor response increased by more than double compared with a good response with 95% CI 1.28 – 3.92 (P = 0.005).

Legal entity responsible for the study: The National Cancer Institute
Funding: The National Cancer Institute, Cairo University
Disclosure: All authors have declared no conflicts of interest.
Phase 3 trial of paximadone plus rituximab versus gemcitabine plus rituximab in treating relapsed/refractory transplant-ineligible aggressive non-Hodgkin’s lymphoma


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Background: Aggressive non-Hodgkin’s lymphoma (NHL) comprises 44% of all NHL, and diffuse large B-cell lymphoma (DLBCL) is the most common subtype. Anthracycline-based regimens are the standard of care for front-line therapy. There is currently no standard treatment for relapsed/refractory (R/R) aggressive NHL beyond second-line for patients who are not transplant-eligible. Paximadone is a novel an-ahtnacenedione designed to have less cardiac toxicity than the anthracyclines. A phase 3 study of monotherapy with paximadone versus comparator gave results that were sufficiently promising for conditional European approval for the treatment of multiply R/R aggressive B-cell NHL. We set up a phase 3 trial to explore the efficacy of combining paximadone with rituximab, which responds to one of the European post-authorisation measures.

Trial design: We are enrolling adult patients with DLBCL or follicular grade 3 lymphomas who have relapsed after at least one multagent chemotherapy regimen. All patients are ineligible for stem cell transplantation, with Eastern Cooperative Oncology Group score ≤2 and normal cardiac function. Centers have been opened in the USA and Europe (Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, Italy, Poland, Romania, Russia, Slovakia, Spain, UK, and Ukraine). Included patients will be randomly allocated to receive up to six 28-day cycles of paximadone (50 mg/m² IV on days 1, 8, 15) plus rituximab (375 mg/m² IV on day 1) or gemcitabine (1000 mg/m² IV on days 1, 8, 15) plus rituximab (375 mg/m² IV on day 1). To complete 6 cycles, patients who discontinue one study drug due to toxicity may continue with the other assigned study drug. The primary endpoint is progression-free survival; secondary endpoints include overall survival, overall response rate, and safety. Recruitment is ongoing.

Clinical trial identification: NCT01321541

Legal entity responsible for the study: CTI Biopharma Corp

Funding: CTI Biopharma Corp


Honoraria, research grants, or both from Servier or CTI Biopharma Corp. T. Devries, J.P. Dean

Employer of CTI Biopharma Corp. M. Pavlyuk, N. Failloux: Employer of Servier
ZUMA-1: A phase 2 multi-center study evaluating anti-CD19 chimeric antigen receptor (CAR) T cells in patients with refractory aggressive non-Hodgkin lymphoma (NHL)

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3. Department of Lymphoma/Myeloma, University of Southern California, Los Angeles, CA, USA
4. Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
5. Department of Medicine, University of Rochester Medical Center, Rochester, NY, USA
6. Department of Hematology and Oncology, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA
7. Clinical Divisions, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ, USA
8. Moores Cancer Center, University of California San Diego, La Jolla, CA, USA
9. Department of Hematology and Stem Cell Transplantation, Division of Hematology/Oncology, Department of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA
10. Division of Blood and Marrow Transplantation, Stanford University School of Medicine, Stanford, CA, USA
11. Division of Hematology & Oncology, Department of Medicine, and Department of Pathology & Laboratory Medicine, University of California, Los Angeles, CA, USA
12. Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
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14. Department of Hematology & Oncology, Sarah Cannon Research Institute, Nashville, TN, USA
15. Division of Hematology, Oncology and Blood and Marrow Transplantation, University of Iowa Hospitals and Clinics, Iowa City, IA, USA
16. Cardinal Bernardin Cancer Center, Loyola University Medical Center, Maywood, IL, USA
17. Kite Pharma, Santa Monica, CA, USA

Background: Diffuse large B-cell Lymphoma (DLBCL) is 30%-58% of all NHL and has an incidence of 5.8/100,000 in Europe (Tilly et al. Ann Oncol 2015). KTE-C19 is an antigen-specific T cell therapy with CD28/CD3 signaling domains centrally manufactured using a streamlined 6-8 day process (Better et al. ASCO 2014). The multicenter phase 1 portion of ZUMA-1 found that KTE-C19 was safe for further study and had a 50% overall response rate (ORR) in patients with aggressive lymphoma, including DLBCL.

Trial design: Approximately 112 patients with refractory, aggressive NHL will be enrolled into cohort 1 (approximately 72 patients with DLBCL or diffuse large B cell lymphoma (DLBCL) or transformed follicular lymphoma). Patients will receive a fixed dose of 30 mg/m2/day fludarabine and 500 mg/m2/day cyclophosphamide conditioning chemo (chemo) x 3 days followed by a single infusion of KTE-C19 at a target dose of 2 x 10^9 anti-CD19 CAR T cells/kg. Eligible patients will have chemo-refractory disease (progressive disease [PD] or stable disease to most recent chemo or PD/recurrence ≤12 months of prior autologous stem cell transplant), ≥18 years old, ECOG PS 0-1, adequate marrow, renal, hepatic, and cardiac function, and prior anti-CD20 monoclonal antibody and an anthracycline-containing chemo regimen. Patients with prior CAR T cell or other genetically modified T cell therapy, clinically significant infection, or current or history of central nervous system lymphoma are ineligible. The primary endpoint is to evaluate KTE-C19 efficacy by ORR (CR + partial remission). Key secondary objectives include duration of response, progression-free survival, overall survival, safety, pharmacokinetics, pharmacodynamics, and predictive biomarker analyses. The study is planned at approximately 25 sites in the US and EU. Accrual began November 2, 2015.

Clinical trial identification: NCT02348216

Legal entity responsible for the study: Kite Pharma

Funding: Kite Pharma


ZUMA-2: A phase 2 multi-center study evaluating the efficacy of KTE-C19 (Anti-CD19 CAR T cells) in patients with relapsed/refractory Mantle cell lymphoma (R/R MCL)

1. Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
2. Department of Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, FL, USA
3. Department of Hematology & Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA, USA
4. Moores Cancer Center, University of California San Diego, La Jolla, CA, USA
5. Kite Pharma, Santa Monica, CA, USA

Background: R/R MCL is an aggressive, generally incurable, B cell malignancy, representing approximately 6% of non-Hodgkin lymphomas with an incidence rate of 0.45/100,000 in Europe (San et al. Blood 2010). An ongoing study at the National Cancer Institute (NCI) using anti-CD19 CAR T cells with CD28/CD3ζ signaling domains showed durable remissions in patients with R/R B cell malignancies, including MCL (Kochenderfer et al. J Clin Oncol 2015; NCT00924326). KTE-C19 is an autologous, anti-CD19 CAR T cell therapy that utilizes the construct investigated in the NCI study and manufactured in a streamlined 6-8 day process. Here, we describe a phase 2 study evaluating KTE-C19 in patients with R/R MCL.

Trial design: We plan to enroll approximately 70 patients with R/R MCL for treatment with a fixed dose of 30 mg/m2/day fludarabine and 500 mg/m2/day cyclophosphamide conditioning chemotherapy followed by a single infusion of KTE-C19 at a target dose of 2 x 10^9 anti-CD19 CAR T cells/kg. Patients should have R/R disease with up to 5 prior therapies, which must have included an anthracycline- or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy, andibrutinib. Additional inclusion criteria include age ≥18 years old, ECOG PS 0-1, and adequate marrow, renal, hepatic, and cardiac function. Patients with prior CAR T cell or other genetically modified T cell therapy, clinically significant infection, or

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: I.M. Michot: Advisory board member Bristol Myers Squibb. W. Ding: Corporate-sponsored research. Merck, research funding. A. Balakumaran, M. Mariniello, S. Chlosta, Y. Zhang: Employee of Merck & Co, Inc. All other authors have declared no conflicts of interest.

References:
Kochenderfer et al. J Clin Oncol 2015; NCT00924326. KTE-C19 is an autologous, anti-CD19 CAR T cell therapy that utilizes the construct investigated in the NCI study and manufactured in a streamlined 6-8 day process. Here, we describe a phase 2 study evaluating KTE-C19 in patients with R/R MCL.

Trial design: We plan to enroll approximately 70 patients with R/R MCL for treatment with a fixed dose of 30 mg/m2/day fludarabine and 500 mg/m2/day cyclophosphamide conditioning chemotherapy followed by a single infusion of KTE-C19 at a target dose of 2 x 10^9 anti-CD19 CAR T cells/kg. Patients should have R/R disease with up to 5 prior therapies, which must have included an anthracycline- or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy, andibrutinib. Additional inclusion criteria include age ≥18 years old, ECOG PS 0-1, and adequate marrow, renal, hepatic, and cardiac function. Patients with prior CAR T cell or other genetically modified T cell therapy, clinically significant infection, or
current or history of central nervous system lymphoma or comorbidities are not allowed. The primary objective is to evaluate the safety and efficacy of KTE-C19, as measured by overall response rate (complete remission + partial remission). Key secondary objectives include describing duration of response, progression-free survival, overall survival, pharmacokinetics, pharmacodynamics, and predictive biomarker analyses. The study is planned at approximately 25 sites in the US and EU. Accrual began on November 9, 2015. Clinical trial information: NCT02601313.

Clinical trial identification: NCT02050133
Legal entity responsible for the study: Kite Pharma
Funding: Kite Pharma

A randomized comparative study of PF-05280586 (a potential biosimilar) vs rituximab for patients with CD20+ low tumor burden, follicular lymphoma

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Background: Use of single-agent rituximab may provide a useful alternative to watching and waiting by delaying the time to initiation of chemotherapy in patients with low tumor burden follicular lymphoma (LBFI). However, access to biologics like rituximab can be restricted. Biosimilars to rituximab represent a potential opportunity to increase patient access and lower treatment cost. PF-05280586, a proposed biosimilar to rituximab, has the same primary amino acid sequence, similar physicochemical and in vitro functional properties, and demonstrated similarity to rituximab in nonclinical evaluations and clinical trials.

 Trial design: Patients (N = 394) will be stratified by risk level and randomized (1:1; double-blind) to 4-weekly doses of IV PF-05280586 or rituximab-EU (375 mg/m2 of body surface area). The primary endpoint is overall response rate at WK 26. Secondary endpoints include safety, time to treatment failure, progression-free survival, complete remission rate at WK 26, response duration, overall survival, PK, CD19+ B-cell depletion, and immunogenicity. Eligible patients are ≥18 yrs with histologically confirmed, Grade 1-3a, low tumor burden, CD20+ follicular lymphoma with no elements of diffuse large B-cell lymphoma, Ann Arbor Stage II, III, or IV, and ECOG status of 0–1. Key exclusion criteria are: patients who are not candidates for rituximab monotherapy; evidence of histologic transformation to high-grade or diffuse large B-cell lymphoma; Ann Arbor Stage II, III or IV; and ECOG confirmed, Grade 1–3a, low tumor burden, CD20+ follicular lymphoma with no elements of diffuse large B-cell lymphoma; Ann Arbor Stage II, III or IV; and ECOG confirmed, Grade 1–3a, low tumor burden, CD20+ follicular lymphoma with no elements of diffuse large B-cell lymphoma; Ann Arbor Stage II, III or IV; and ECOG confirmed, Grade 1–3a, low tumor burden, CD20+ follicular lymphoma with no elements of diffuse large B-cell lymphoma; Ann Arbor Stage II, III or IV; and ECOG confirmed, Grade 1–3a, low tumor burden, CD20+ follicular lymphoma with no elements of diffuse large B-cell lymphoma.

Clinical trial identification: NCT0221363
Legal entity responsible for the study: Pfizer Inc.
Funding: Pfizer Inc.

Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (cHL): randomized phase 3 KEYNOTE-204 study

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Background: Patients with cHL who relapse after autologous stem-cell transplantation (auto-SCT) or are ineligible to proceed to transplantation have poor prognosis. The PD-1 ligands, PD-L1 and PD-L2, are frequently overexpressed in relapsed or refractory (R/R) cHL, and this is typically associated with chromosome 9p24.1 amplification. In the phase III KEYNOTE-015 study, PD-1 blockade with pembrolizumab (pembro) demonstrated an objective response rate (ORR) of 65% in heavily pretreated patients with cHL. KEYNOTE-204 (NCT02684292) is a randomized, international, open-label phase 3 study designed to compare the efficacy and safety of pembro versus brentuximab vedotin (BV) in patients with R/R cHL.

Trial design: This trial will enroll patients ≥18 years with R/R cHL who (1) have failed to achieve a response or progressed after auto-SCT and have not received prior BV; or (2) are not auto-SCT candidates because of chemoresistant disease (unable to achieve complete or partial remission to salvage chemotherapy), advanced age, or comorbidities, and have received ≥2 prior multi-agent chemotherapy regimens that did not include BV. ≥300 patients will be randomized 1:1 to receive either pembro 200 mg Q3W or BV 1.8 mg/kg Q3W for up to 35 cycles or until documented disease progression, unacceptable toxicity, or investigator decision. Response will be assessed every 12 weeks by EET/CIT scans per Revised Response Criteria for Malignant Lymphoma from the International Working Group (IWG) by central imaging vendor review. Primary end points are PFS and OS, secondary end points are ORR and complete remission rate. The primary assessment of efficacy end points will be based on blinded independent central review according to the IWG criteria; secondary/exploratory analyses of efficacy end points will be conducted using investigator assessment. Exploratory end points include duration of response, primary progression, and comparison of ORR in patients with PD-L1-positive versus PD-L1-negative lymphoid tumors. Enrollment to KEYNOTE-204 is ongoing.

Clinical trial identification: NCT02684292
Legal entity responsible for the study: Merck & Co., Inc.
Funding: Merck & Co., Inc.
Disclosure: Y. Zhu, A.D. Ricart, A. Balakumaran: Employee and stock ownership at Merck & Co., Inc. All other authors have declared no conflicts of interest.

Phase 3 study of quizartinib (AC220) monotherapy vs salvage chemotherapy (SC) in patients (pts) with FLT3-ITD+ acute myeloid leukemia (AML) refractory to or relapsed (R/R) after 1st-line treatment with or without hematopoietic stem cell transplant (HSCT) consolidation: the QUANTUM-R study

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Background: Approximately 25% of pts with AML have FLT3-ITD internal tandem duplications (ITD) mutations, which are key oncogenic drivers of the disease. FLT3-ITD+ AML is associated with poorer prognosis, decreased response to salvage therapy, increased risk of relapse, and shorter survival than FLT3-ITD–negative disease. Currently, there are no approved therapies targeting FLT3-ITD mutations, and improved therapeutic options are needed in this setting. Quizartinib is an oral, high-potent, and selective inhibitor that targets FLT3-ITD mutations. Previous studies of quizartinib monotherapy have reported composite complete response rates up to 46% in pts with R/R FLT3-ITD AML (Cortes J, EJ Hem Oncol. 2013;31:1304–1367; Levis M, ASCO 2014 [abstract 7093]). Here, we describe QUANTUM-R, a multicenter, open-label, randomized phase 3 study (NCT02039726) to determine the efficacy of quizartinib in pts with FLT3-ITD+ AML who are R/R within 6 months after last-line therapy.
**Trial design:** Eligible pts include adults ≥ 18 years with FLT3-ITD-positive AML in first relapse or refractory to prior therapy, with or without HSCT. Pts with prior exposure to quizartinib or other targeted FLT3-ITD inhibitors are excluded from this study. Approximately 326 pts will be randomized 2:1 to receive quizartinib or SC selected for each pt by the investigator prior to randomization. Options for SC regimens include mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC); or fludarabine, cytarabine, and granulocyte colony stimulating factor with idarubicin (FLAG-IDA); or low-dose cytarabine (LoDAC). Quizartinib will be administered until lack of benefit or HSCT. The primary objective of this study is to determine whether quizartinib prolongs overall survival compared with SC in pts with R/R FLT3-ITD-positive AML. The secondary objective is to determine event-free survival with quizartinib vs SC. This study is currently recruiting pts.

**Clinical trial identification:** NCT02039726

**Legal entity responsible for the study:** Daiichi Sankyo, Inc.

**Funding:** Daiichi Sankyo, Inc.

**Disclosure:** J. Cortes: Consulting/Advisory Role with ARIAD, Ambit Pharmaceuticals, Astellas and Novartis. Research funding received from ARIAD, Ambit, Astellis, Arog, Flexus and Novartis. G. Gammon: Employee of Daiichi Sankyo. S. Khaled: Honorarium, consulting/advisory role, speakers’ bureau, travel, accommodations, expenses with Alexion; Research funding received from Ambit, MEL, Sanofi, Omeros. G. Martinelli: Consulting or Advisory Role with ARIAD, Amgen, Pfizer, and Roche; Speakers’ Bureau with Novartis and IMS. A. Kramer: Honoraria received from Teva; Consulting/Advisory Role with NeoOncology, Research funding received from Bayer, Merck Serono, Travel, Accommodations, Expenses received from Teva. B. Steffen: Travel, accommodations, expenses received from Novartis, GSK, Astellas. D. Hogg: Consulting or advisory role with Sanofi; Travel, accommodations, expenses from Roche. B.A. Jonas: Consulting – Regent Honoraire/Speaking – Celgene Research Funding – Pharmacyclics. H. Dombret: Honoraria received from Abrit and Daiichi Sankyo, Consulting/Advisory Role with Ambit and Daiichi Sankyo. A. Perl: Consulting fees received from, Daiichi Sankyo, Astellas Pharmaceuticals, Seattle Genetics, Asana Biosciences, and Actinium Pharmaceuticals.
head and neck cancer

Updated safety and efficacy of durvalumab (MEDI4736), an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort

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Background: Recurrent and metastatic (R/M) SCCHN outcomes are generally poor and new treatments are needed. An ongoing phase I/II multicenter, open-label study (NCT01695652) is evaluating the safety and efficacy of durvalumab (D), a human IgG1 mAb that blocks PD-L1 binding to PD-1 with high affinity and selectivity, in multiple solid tumor types including SCCHN. PD-L1 is expressed in SCCHN tumors and is associated with response to anti-PD-L1 treatment.

Methods: Patients with R/M SCCHN, an ECOG of 0 or 1, and no prior anti-PD-L1/PD-L2 exposure are eligible. D is given every 2 weeks IV at 40 mg/kg for 12 weeks. Retreatment is permitted upon progression after 12 months. Safety data and efficacy data (Dosis and PFS/OS) included have more mature follow up than previously reported (Segal, N et al. Poster presented at ASCO 2015, 3011).

Results: As of 29 Apr 2016, 62 pts (mean age 58 years [range 24-96]; 86% male; 63% current/prior smokers; ECOG 0/1: 98%/8%; HPV pos/neg/unk: 40%/30%/30%, PD-L1 positive/unknown: 34%/65%, had received a median of 3 prior systemic treatments (1-5)). Median duration of follow-up was 25.0 (range 1.4 – 51.8) months. The most frequent drug-related AEs were fatigue (18%), diarrhea (8%), and nausea (8%). Five (8%) had AEs ≥3 and there were no drug-related AEs leading to death. Among seven responders, six patients had DoR for >12 months with longest DoR being 19.8 months. Six and 12-month OS is 62% (95% CI 48, 74) and 42% (95% CI 30, 55), respectively. Preliminary analysis revealed no clear difference in OS by PD-L1 status.

Conclusions: In this updated report, the safety profile of D in SCCHN is consistent with previous reports. Responses are durable; landmark OS rates are encouraging in this heavily pre-treated population. A registration program is underway in pts with SCCHN for D alone and in combination with tremelimumab.

Clinical trial identification: NCT01695362

Legal entity responsible for the study: MedImmune LLC

Funding: MedImmune


Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 100 randomized trials and 19,248 patients, on behalf of MACH-NC group


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Background: Our previous meta-analysis showed that concomitant chemotherapy (CT) improved overall survival (OS) in patients with non-metastatic head and neck squamous cell carcinoma (HNSCC). The purpose study was to update patient follow up, gather data on toxicity and include randomized trials conducted up to 2010. Methods: This individual patient data meta-analysis included trials comparing loco-regional treatment (LRT) vs LRT + induction CT to RT + concomitant (or alternating) CT in non-metastatic HNSCC patients and included conducted between 1965 and 2010. A fixed effect model was used. Log-rank test, stratified by trial, was used to compare treatments. OS was the primary endpoint. Results: 15 new trials (2,574 patients) were included. Updated data were obtained for 11 additional trials. For the comparison of LRT vs. LRT + CT, 94 trials (18,394 patients) with median follow up of 6.7 years were analyzed. The most frequent tumor site was oropharynx (35%). Stage III and IV tumors represented 28% and 63% of patients. The addition of CT improved OS with a hazard ratio (HR) [95% confidence interval] of 0.89 [0.86; 0.92], p < 0.0001. There was a significant interaction between treatment effect and the timing of RT, the benefit being limited to concomitant CT (p = 0.0001), with a HR of 0.83 [0.79; 0.87], translating into a 5-10-year absolute survival benefit of 6.3 (3.4%). The addition of induction CT did not increase OS, with a HR of 0.97 [0.91; 1.03]. Interaction test performed in recent concomitant trials revealed a trend toward decreased effectiveness of increasing age (p for trend = 0.06, HR of 1.09 [0.81; 1.41] for age ≥ 70 vs performance status (p for trend = 0.07, HR of 0.93 [0.73; 1.19] for PS ≥ 2). The analysis of 8 trials (1,214 patients) comparing induction CT to RT + RT or concomitant CT confirmed the superiority of concomitant CT (HR of 0.85 [0.75; 0.96], p = 0.008) and progression-free survival (HR of 0.85 [0.75; 0.96], p = 0.008).

Conclusions: This update of the MACH-NC meta-analysis confirms the superiority of concomitant CT for locally advanced HNSCC with longer follow up, when compared to induction treatment. Study of patterns of relapse and toxicity is ongoing.

Legal entity responsible for the study: N/A
Surrogate endpoints for overall survival in loco-regionally advanced nasopharyngeal carcinomas: Results from the individual patient data meta-analysis MAC-NPC2


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Background: Our objective was to evaluate progression-free survival (PFS) and distant metastasis-free survival (DMFS) as surrogate endpoints for overall survival (OS) in randomized trials of chemotherapy in loco-regionally advanced nasopharyngeal carcinomas (LANPC).

Methods: Individual patient data were obtained from 19 trials of the updated Meta-Analysis of Chemotherapy in Nasopharyngeal Carcinoma (MAC-NPC) plus one additional trial (total: 5,144 patients). Surrogacy was evaluated at the individual level using a rank correlation coefficient ρ and at the trial level using a correlation coefficient R 2 between surrogates and endpoint. OS was defined as death from any cause and PFS and DMFS as the time to progression to any cause of death or metastatic disease, as appropriate.

Results: PFS was strongly correlated with OS at the individual level (p = 0.93, 95% Confidence Interval [CI]: 0.93–0.94) and at the trial level (R 2 = 0.95, 95% CI: 0.94–1.00). For DMFS, the individual level correlation with OS was strong (p = 0.98, 95% CI: 0.98–0.98) at trial level, the correlation was high but the regression adjusted for measurement error could not be computed (unadjusted R 2 = 0.96, 95% CI: 0.94–0.99). In the sensitivity analysis, 2-year PFS was highly correlated with 5-year OS at the individual level (p = 0.89, 95% CI: 0.88–0.90) and at the trial level (R 2 = 0.85, 95% CI: 0.84–1.00). 2-year DMFS was highly correlated with 5-year OS at the individual level (p = 0.93, 95% CI: 0.94–0.95) and at trial level (R 2 = 0.78, 95% CI: 0.63–0.80).

Conclusions: PFS and DMFS are valid surrogate endpoints for OS to assess treatment effect in LANPC and PFS can be measured earlier.

Legal entity responsible for the study: Meta-Analysis Platform of the ‘Ligue Nationale contre le Cancer’, Gustave Roussy Cancer Campus, Villejuif, France.


Disclosure: All authors have declared no conflicts of interest.

PET-CT surveillance for advanced head and neck cancer: a cost-effective alternative to planned neck dissection

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Background: Despite controversy, planned neck dissection (ND) remains standard treatment for patients with locally advanced head and neck squamous cell carcinoma after radical chemoradiotherapy. FDG-PET-CT scanning has demonstrated high negative predictive values for persistent disease, and could thereby enable low risk patients to be spared from unnecessary surgery. Evidence of the cost-effectiveness of PET-CT would provide a cost-effective alternative to planned neck dissection.

Table: 9540

<table>
<thead>
<tr>
<th>Adenoid Cystic Carcinoma (ACC)</th>
<th>Acinic Cell Carcinoma (ACCt)</th>
<th>Muco-epidermoid Carcinoma (MEC)</th>
<th>Ductal Carcinoma (DCA)</th>
<th>Adenoid-Carcinoma (AC-NOS)</th>
<th>Carcinoma NOS (CA-NOS)</th>
<th>Carcinoma ex Plasmocytoid Adenoma (CPA)</th>
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<tbody>
<tr>
<td>Patients GA/tumor</td>
<td>28</td>
<td>1.6</td>
<td>4.0</td>
<td>48</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>Sign. GA Mutation Frequencies</td>
<td>MYB-NFIB FGRFR (C3)</td>
<td>PSEN1</td>
<td>PKN3</td>
<td>ERBB2 RET NF1 BRAF</td>
<td>ERBB2 RET NF1 BRAF</td>
<td>ERBB2 RET NF1 BRAF</td>
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<tr>
<td>TP53</td>
<td>4%</td>
<td>8%</td>
<td>42%</td>
<td>54%</td>
<td>53%</td>
<td>59%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>0</td>
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<td>27%</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td>RET</td>
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<td>0</td>
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<td>2%</td>
<td>2%</td>
<td>0</td>
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<tr>
<td>ETV6-NTRK Fusion</td>
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</tr>
<tr>
<td>BRAF</td>
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</tr>
<tr>
<td>tumor mutation</td>
<td>1%</td>
<td>3%</td>
<td>10%</td>
<td>11%</td>
<td>6%</td>
<td>1%</td>
</tr>
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</table>

| BURDEN (MB) | 30 | 26 | 2 |
| Opportunity for Targeted Therapies | Low | Low | Modest | High | High | High | High |

References:


PET-CT surveillance strategies is limited however, and no evaluations have yet been conducted from a UK perspective. Methods: An economic evaluation was conducted to assess the lifetime cost-effectiveness of PET-CT surveillance versus planned ND from a UK secondary care perspective. Cost and health outcomes associated with the initial 6-month treatment period (CRT +/- ND) were derived from individual data on 564 patients from a recent UK multicentre randomised controlled trial (PET-Neck). Subsequent outcomes were derived using a constructed Markov model to track patients through four health states: disease-free, local recurrence, distant recurrence and dead. Model inputs were derived from trial data and literature sources. Results: PET-CT surveillance results in a lifetime cost saving of £1,485 (95% CI: £2,415 to £159) and health gain of +0.13 (95% CI: +0.49 to +0.79) quality-adjusted life-years (QALYs) per patient. The intervention therefore demonstrates standard care, being more effective and less costly, with an incremental net benefit (INB) of +0.21 QALYs (95% CI: +0.41 to +0.01). At a willingness-to-pay per QALY of £20,000, PET-CT is associated with a 75% probability of being cost-effective, dropping to 68% at a £100,000/QALY threshold. The intervention remained cost-effective when considering a broader NHS and personal social services perspective; however, uncertainty around the mean cost-effectiveness values was wide. Conclusion: PET-CT surveillance appears to be cost-effective, leading to expected lifetime cost savings and a marginal health increment. There is significant uncertainty in the longer term which may warrant additional survivorship research.

Clinical trial identification: ISRCTN13735240

Legal entity responsible for the study: Warwick Medical School.

Funding: National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number 07/032/129).

Disclosure: All authors have declared no conflicts of interest.

Table: 953PD

<table>
<thead>
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<th>Database cutoff</th>
<th>HR (Cox model 95% CI)</th>
<th>(bootstrapping 95% CI)</th>
</tr>
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<tr>
<td>ITT*</td>
<td>IPE</td>
<td>RPSFT</td>
</tr>
<tr>
<td>2012 Aug</td>
<td>0.80 (0.54–1.19)</td>
<td>0.70 (0.47–1.04)</td>
</tr>
<tr>
<td>2013 May</td>
<td>0.88 (0.63–1.24)</td>
<td>0.79 (0.57–1.11)</td>
</tr>
<tr>
<td>2015 Jul</td>
<td>0.92 (0.71–1.21)</td>
<td>0.80 (0.61–1.05)</td>
</tr>
</tbody>
</table>

*Unadjusted for treatment switch

Clinical trial identification: NCT00895674

Legal entity responsible for the study: N/A

Funding: Bayer Healthcare Pharmaceuticals

Disclosure: M. Brose: Received consultancy fees/honorarium and research support from Bayer HealthCare Pharmaceuticals; consultancy fees and research support from Exelixis; consultancy fees from Onyx Pharmaceuticals; and research support from Eisai, Novartis, & Roche/Genentech. B. Jazarj: Received honorarium and research support from Bayer Healthcare Pharmaceuticals; consultancy fees/honorarium from AstraZeneca and Sobi; and honorarium from Eisai, Ipsen, Novartis, Onex, Pfizer, Roche, and Sanoft. R. Elisei: Consultancy fees/honorarium and research support from Bayer Healthcare Pharmaceuticals; and consultancy fees/honorarium from AstraZeneca and Genzyme. L. Barthol: Consultancy fees and research support from Bayer Healthcare Pharmaceuticals; and consultancy fees from AstraZeneca. C. de Frochardiere: Consultancy fees/honorarium and research support from Bayer Healthcare Pharmaceuticals; consultancy fees/honorarium from AstraZeneca and Genzyme. C. M. Schumburger: Consultancy fees and research support from Bayer Healthcare Pharmaceuticals; and consultancy fees/honorarium and research support from AstraZeneca and Genzyme/Sanoft; and a grant from Roche, F. Pacini: Honorarium and research support from Bayer Healthcare Pharmaceuticals; R. Paschke: Research support from Bayer Healthcare Pharmaceuticals. S. Sherman: Research support from Bayer Healthcare Pharmaceuticals; Genzyme, and Pfizer; consultancy fees/honorarium and research support from Amgen; consultancy fees/honorarium from AstraZeneca, Eisai, Exelixis, Lilly, NovoNordisk, Varaycey, Onyx, and Roche; J. Smitt: Member of the DECISION steering committee and has received honorarium and research support from Bayer Healthcare Pharmaceuticals. J. Chong, G. Meinhardt: Employee of Bayer Healthcare Pharmaceuticals. M. Schumburger: Received consultancy fees and research support from Bayer Healthcare Pharmaceuticals and Eisai; consultancy fees/honorarium and research support from AstraZeneca and Genzyme/Sanoft; consultancy fees from Exelixis; and consultancy fees/honorarium from Sobi. C. Kappeler: Employee of Bayer Pharma AG. All other authors have declared no conflicts of interest.

A comparative study of PD-L1 diagnostic assays in squamous cell carcinoma of the head and neck (SCCHN)

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Background: PD-1/PD-L1 directed antibodies are emerging as effective therapeutics in multiple oncology settings. In the SCCHN Checkmate 141 study, improved efficacy with nivolumab, a PD-1 targeted therapy, was observed in pts with tumour PD-L1 expression ≥1% versus pts with PD-L1 expression below this cut off. Multiple diagnostic PD-L1 tests are available using different antibody clones, different staining protocols and different cut offs. A better understanding of the technical performance of these assays will allow appropriate interpretation of clinical outcomes with different drugs. Methods: 108 tumour biopsy samples from stage I-IV SCCHN pts, obtained from a commercial source and including HPV positive and HPV negative, were assessed using 3 PD-L1 diagnostic assays: the Ventana SP263 assay currently being used in durvalumab (anti-PD-L1) clinical trials, the Dako 28-8 and Dako 22C3 assays which are commonly used in tumour PD-L1 testing, respectively. Assays were performed in an accredited laboratory, following the device protocol. Concordance between tumour membrane staining was assessed across a range of clinically relevant cut offs, including ≥1%, ≥10% and ≥25%. Lower 95% CI were calculated using the Clopper-Pearson method.

Results: Data indicated strong association, with a Spearman correlation coefficient of ≥0.9 for each pairwise comparison. Overall percent agreement (OPA) of ≥90% was reached in ITT, a trend in OS prolongation favoring SOR was observed consistently over successive time points. OS crossover adjustment results suggest that the true OS treatment effect may be larger than seen in the ITT analysis. The IPE method appears to produce more stable adjusted HRs across the 3 time points than RPSFT. These results should be considered as exploratory.
Development of a predictive radiomics signature for response to immunotherapy checkpoint inhibitors (ICIs) in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (RM-SCCHN)

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Disclosure: L.L. Siu: Research funding from Merck to conduct clinical trials. All other authors have declared no conflicts of interest.

Table: 959PD

<table>
<thead>
<tr>
<th>Assay cut off</th>
<th>OPA (%)</th>
<th>Lower 95% CI</th>
<th>OPA (%)</th>
<th>Lower 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1%</td>
<td>91.7</td>
<td>85.9</td>
<td>96.3</td>
<td>91.7</td>
</tr>
<tr>
<td>≥10%</td>
<td>92.6</td>
<td>87.0</td>
<td>95.4</td>
<td>90.5</td>
</tr>
<tr>
<td>≥25%</td>
<td>94.4</td>
<td>89.3</td>
<td>97.2</td>
<td>93.0</td>
</tr>
</tbody>
</table>

Conclusions: This study indicates that the SCCHN patient population defined by pre-treatment baseline CT images can be classified with a high degree of confidence using radiomics features derived from this imaging modality. The development of such a predictive radiomics signature has the potential to improve patient outcomes by enabling more personalized treatment decisions. Further validation and clinical trials are needed to establish the utility of this approach in the management of SCCHN.

Legal entity responsible for the study: AstraZeneca PLC

Funding: Merck & Co., Inc.

Disclosure: All authors have declared no conflicts of interest.

References:
Tumor growth rate analysis of progression-free survival (PFS) and overall survival (OS) for thyroid cancer patients receiving placebo or sorafenib in the phase 3 DECISION trial

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Background: In the randomized, controlled phase 3 DECISION trial (NCT00895674), sorafenib (SOR) significantly improved progression-free survival (PFS) vs placebo (PLC) in patients with radioactive iodine refractory differentiated thyroid cancer (HR, 0.587; p < 0.0001). Here we report the analysis exploring prognostic characteristics of tumor growth rate (TGR) for PFS and OS.

Methods: The primary endpoint of DECISION was PFS and OS was a secondary endpoint. Target lesions were assessed by central radiologic review every 8 weeks based on RECIST 1.0 criteria. Changes in target lesions over time were approximated by a parabola-like 3-parametric model. TGR was defined as % change per month of sum of target lesion diameters (SLD). To explore the association between TGR and PFS and OS, values of early TGR were split into quartiles separately by treatment arm. PFS (cutoff in 2012) and OS (cutoff 2015) were compared in each subgroup population by median times derived from KM curves and from modeling with a Weibull distribution. Correlation of TGR with maximum reduction in SLDs was examined.

Results: TGR subgroup statistics and median times of PFS and OS are shown in table 1. For these endpoints there is no simple proportional relation between TGR and median PFS or OS times. Better prognosis for PFS and OS is associated with Q2 or Q3 TGR quartiles. Early TGR values close to zero indicate a better prognosis. TGR and SLD show a high correlation.

Conclusions: In this exploratory analysis, stabilization of tumor lesions at treatment start seems to be associated with better PFS and OS outcomes than a pronounced early reduction of tumor lesion sizes. TGR may be an additional efficacy parameter to consider when monitoring SOR treatment.

Table: 958P Weibull model of KM curves; durations in months

<table>
<thead>
<tr>
<th>Quartile</th>
<th>PLC</th>
<th>Sorafenib (SOR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med early TGR</td>
<td>14,982</td>
<td>14,983</td>
</tr>
<tr>
<td>Med PFS</td>
<td>5.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Med OS</td>
<td>40.3</td>
<td>47.6</td>
</tr>
</tbody>
</table>

Clinical trial identification: NCT00895674

Legal entity responsible for the study: N/A

Funding: Bayer Healthcare Pharmaceuticals

Disclosure: C. Kappeler: Employee of Bayer Pharma AG. G. Meinhardt: Employee of Bayer Healthcare Pharmaceuticals; R. Elisei: Consultancy fees/honorarium and research support from Bayer Healthcare Pharmaceuticals; and consultancy fees/honorarium from AstraZeneca and Gynемые. M. Brose: Consultancy fees/honorarium and research support from Bayer Healthcare Pharmaceuticals; consultancy fees/research support from Exelixis, consultancy fees from Onyx Pharmaceuticals; and research support from Eisai, Novartis, and Roche/Genentech. M. Schlumberger: Consultancy fees/research support from Bayer Healthcare Pharmaceuticals and Eisai; consultancy fees/honorarium and research support from AstraZeneca and Genzyme-Sanoft; consultancy fees from Exelixis; and consultancy fees/honorarium from Sobi.

PIK-ORL: A phase II, multicenter trial aiming to evaluate BKM120 in monotherapy in patients (pts) with metastatic/recurrent head and neck squamous cell carcinoma (HNSCC) after failure of platin and cetuximab or anti-EGFR-based therapy


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Background: The PI3K/AKT pathway activation is an early event in HNSCC and an independent marker of poor outcome that seems to be involved in resistance to cetuximab. BKM120 is an oral, pan-Class I PI3K inhibitor that inhibits tumor growth in HNSCC xenografts.

Methods: This Phase II trial evaluates the clinical benefit of BKM120 (100mg/d, po) in 2 parallel cohorts of HNSCC pts with or without mutation in PIK3CA. Eligible pts progressed after platin and cetuximab or anti-EGFR therapy, and had documented PIK3CA status (exons 9 and 20). The primary endpoint was 2-month Disease Control Rate (DCR2m) as per RECIST 1.1. Secondary endpoints were ORR, PFS, OS, and safety. Blood and tumor samples were obtained for pharmacodynamics (PD). Imaging data were centrally reviewed. Considering that BKM120 would be uninteresting if DCR2m ≤ 10% and promising if ≥ 30% and using Simon’s optimal two-stage design (5% unilateral, power 90%), 7/8 pts were required for each cohort. Only results of the cohort without PIK3CA mutation are presented.

Results: 36 HNSCC pts without PIK3CA mutation (median age: 58.6 yrs) received at least one dose of BKM120. They were heavily pretreated (33% with at least 3 previous lines). Median treatment duration was 8 wks (min-max: 4-53.9 wks). At the end of 2nd Simon’s Stage, the DCR2m was 38.9% (14/36Pts). No OR was observed. The most common related AE (>25%) included hyperglycemia, anemia, depression, lymphopenia, rena, leucocyte decrease, hematocrit decrease, nausea and diarrhea. 20 pts (53.6%) presented at least one related AE ≥ Grade 3 (≥5% hyperglycemia, lymphopenia, anemia, Na or K decrease) and 10 pts (27.8%) prematurely discontinued BKM120 due to an AE. 11pts (30.6%) experienced a related SAE, including 3 SUSARs (1 fatal hyperglycemic coma, 1 death of uncertain relationship, 1 severe dehydration). PFS, OS and PD data will be presented at the meeting. Cohort with PIK3CA mutation is ongoing (n = 17).

Conclusions: BKM120 deserves further investigation in relapsing HNSCC pts without PIK3CA mutation, nevertheless with close monitoring of metabolic tolerance.

Clinical trial identification: NCT01737450

Legal entity responsible for the study: Centre Leon Bérard

Funding: Institut National du Cancer et Fondation ARC

Disclosure: All authors have declared no conflicts of interest.

PI3KCA mutation, nevertheless with close monitoring of metabolic tolerance.

Causes of death statistics underestimate the burden of head and neck (H&N) cancers: a nationwide study from France in 2008-2012 (EPICORL study)

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Background: Patients with H&N cancer carry the highest risk of secondary primary cancers. Determining the underlying cause of death is conflicting in presence of multiple primary cancer sites, and the actual burden of H&N cancers may be underestimated by causes of death statistics.

Methods: Using the French National Hospital Discharge (PMSI) database, we identified all adult patients residing in Metropolitan France and diagnosed with H&N cancer (ICD-10: C00-C06; C09-C14; C30.0; C31; C32) in 2008-2012. Overall death was ascertained from in-hospital mortality with use of imputation methods to estimate death outside hospital in 2008-2012. Among deceased patients, we considered advanced H&N cancer (stage III/IV at diagnosis or relapse in the follow-up) as a cause of death. A competing cause of death from other primary cancer sites was categorized...
according to its timing relative to the index date of H&N cancer: former (≤60 days), synchronous (60 to 180 days), or metachronous (<180 days) cancers. Study results were compared to National causes of death statistics (CDEPCD) with use of the same ICD-10 definitions.

Results: Of 131,965 French patients identified with H&N cancer in 2008-2012, 58,562 (44.4%) died in the same period including 46,463 (79.3%) deaths recorded at hospital. Of 58,562 deceased patients, 50,910 (86.9%) were recorded with advanced H&N cancer and involved 82.4% male patients at a median (SD) age of 64 (15.7-74) at death. Overall, 20,926 (41.1%) patients had another primary cancer site than H&N cancer recorded before death. 4,751 (9.3%) former, 11,030 (21.7%) synchronous, and 5,145 (10.1%) metachronous cancers were recorded with increasing likelihood to be considered as the underlying cause of death. The death toll of H&N cancers represented 9.06% of all-cause mortality (2.65% of all premature deaths before 65 years old) in France and increased annually by 6.1% on average. In National causes of death statistics, only 25,847 deaths were attributed to H&N cancers in 2008-2012 without time trends.

Conclusions: The study results suggest that National causes of death statistics underestimate the burden of H&N cancer. It may be explain by the frequency of secondary primary cancers.

Legal entity responsible for the study: THEN (Translational Health Economics Network)

Funding: MSD France


**Axitinib in recurrent or metastatic nasopharyngeal carcinoma (NPC): final result of a phase 2 clinical trial with pharmacokinetic (PK) correlation**

**Abstract**

**E.P. Hu1, B.B. Ma2, F. Mo3, M.K. Kam1, S.L. Chan1, H.H. Loong2, R. Ho3, S. Leung1, A.D. King3, K. Wang1, A.H. Hu4, G.M. Chan1, C.W. Hui2, G.H. Wong1, A.T.C. Chan1**

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Background: Axitinib is approved in advanced renal cell cancer patients (pts) who failed one prior systemic therapy. It has also demonstrated potent activity in preclinical models of NPC (Cancer Res 2012; 72 (8 Suppl): A1373).

Methods: We conducted a phase 2 clinical trial of axitinib monotherapy in recurrent or metastatic NPC pts who progressed after ≥1 line of platinum-based chemotherapy (CT). Pts with local recurrence or vascular invasion were excluded. Axitinib was started at 5 mg twice daily in continuous 4-week cycles until progression or unacceptable toxicity. Primary endpoint was clinical benefit rate (CBR), defined as % of pts achieving complete response (CR), partial response (PR) or stable disease (SD) by RECIST for ≥12 weeks. Secondary endpoints included time to progression (TTP), overall survival (OS), safety, and PK profile. Simon’s Minimax 2-stage phase 2 design (Po = 0.50, Pi = 0.70, type I error 0.05, power 80%) was used to calculate sample size (n = 37, evaluable for response).

Results: We recruited 48 pts. Median age 52 (22-74) M.F. = 35:5. Pts received a median of 3 lines of prior CT (range 1-6). As of 31 Mar 2016, the median follow up was 36.1 months. Pts received axitinib for a median of 4.5 cycles (range 1-21), with 16 pts (40%) received ≥6 cycles, 7 (18%) pts ≥10 cycles and 2 pts ≥18 cycles. 9 (23%) pts had dose escalation and 12 (30%) had dose reduction. Of 37 pts evaluable for response, 3-month CBR = 78.4% (95% CI: 65-92.1%), 1 confirmed P0, 6 unconfirmed P0, 22 SD). 6-month CBR = 42.4% (30.4-54.6%). Median TTP = 5.0 months (95% CI: 3.8-5.7). Median OS = 18.4 months (6.5-18.6). 1-year survival rate = 45.4%. Treatment-related adverse events by CTCAE, all grades (Gr) in ≥25% of pts included: hand-foot (Gr 3: 3%), hypothyroidism (Gr 3: 4%), fatigue (Gr 3: 3%), hypertension (Gr 3: 3%), diarrhoea (Gr 3: 3%), pain (Gr 3: 3%), mucositis (Gr 3: 0%). All hemorrhages were Gr 1 (15%) or Gr 2 (3%). Diastolic blood pressure ≥ 90 mmHg was significantly associated with better OS (HR 0.3, p = 0.0016). Axitinib PK parameters and correlations with dose, efficacy and toxicity will be presented.

Conclusions: Single agent axitinib achieved meaningful disease control with manageable toxicity in heavily pretreated NPC.

Clinical trial identification: CUCT-NP0022, ClinicalTrials.gov NCT01249547

Legal entity responsible for the study: Comprehensive Cancer Trials Unit, Department of Clinical Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong

Funding: Department of Clinical Oncology, The Chinese University of Hong Kong

Disclosure: All authors have declared no conflicts of interest.

**Table: 962P**

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Notes:
P<0.01 vs PB
P<0.0001 vs PB

Clinical trial identification: NCT01312154

Legal entity responsible for the study: Eisai Inc.

Funding: Eisai Inc.

Disclosure: B. Robinson: Advisory Board member for Eisai, AstraZeneca, Bayer and has served as a board member for MaynePharma. M. Schlumberger: Received grants and personal fees from Eisai Inc. J.L. Withř: Served as an advisory board member for Eisai and Loxo and has consulted for Eisai and Asahi. C.E. Dutchie: Employee of Eisai Inc. T.A. Binder, M. Guo: Employee of Eisai Inc. M. Taylor: Served as an advisory board consultant for Eisai and OINTX. M.K. Krzyzanowska: Served as an advisory board member for Eisai and Bayer, and has received research funding (site PI for clinical trials) for Eisai, AstraZeneca, Exelixis, and Novartis. J. Capdevilla: Served as an advisory board member for Eisai, Bayer, AstraZeneca, and received research funding for Eisai, Bayer, and AstraZeneca. S.I. Sherman: Served as an advisory board member for Eisai and Varacyte, has consulted for Exelixis and Rosetta Genomics, and has received research funding from Genzyme. M. Tahara: Received grants, research support, and honoraria from Eisai Inc., received grants and personal fees from Merck.
Survival of patients with head and neck (H&N) cancers: a nationwide study from France in 2008-2012 (EPICORL study)


Methods: We completed a retrospective cohort study using the French National Hospital Discharge (PMSI) database. We identified all adult patients residing in Metropolitan France and diagnosed with H&N cancer (ICD-10: C00-C06, C39-C41, C30.0, C31.0, C31.2) in 2008-2012. Cancer location and stage (early U1, advanced U2IVB, distant metastatic IVc) were determined at diagnosis. Time to relapse, secondary primary H&N cancer, other primary cancers, Charlson comorbidities were recorded until last hospitalization in 2013. Hazard ratios (HR) for in-hospital death were estimated in a multivariate Cox model with use of time-dependent variables.

Results: 131,965 French adults were identified with H&N cancer in 2008-2012: 79.4% were male with median (IQR) age of 61 (54-71) at diagnosis. Overall survival at 5 years was 33.9% (95% CI, 33.9%-34.4%) over a follow-up of 196,000 person-years. As compared to 23.2% patients with laryngeal cancer, survival was significantly lower for 29.3% patients with oral cavity cancer (HR = 1.25), 19.5% patients with oropharynx cancer (HR = 1.22), or 12.8% patients with hypopharynx cancer (HR = 1.26). As compared to 30.7% patients with early cancer at diagnosis, survival was significantly lower for 12.1% patients with advanced metastasis (HR = 3.02) and 35.2% patients with advanced cancer (HR = 1.76). The relapse rate was 22.8% in patients with early cancer and 37.9% in patients with advanced cancer, with significantly lower survival (HR = 6.67). Secondary primary H&N cancers were detected in 6.1% patients at diagnosis (HR = 1.15) and 2.3% patients in the follow-up (HR = 1.79). About 60% had at least one primary cancer cared in the study period (including 10.1% lung. HR = 1.71). About 52% patients had other severe comorbidities incurring significantly lower survival.

Conclusions: This is the first national study on the survival of patients with H&N cancer in France. Relapse had the strongest impact on prognosis. In addition, about two-thirds patients had another primary cancer or severe comorbidities worsening prognosis.

Legal entity responsible for the study: THEN (Translational Health Economics Network)
Funding: MSD France

Molecular profiling of locally advanced/metastatic oesophageal and nasopharyngeal carcinomas

Z. Gatalica, A. Ghazalpour, J. Swensen, R. Bender, S. Vranic, R. Feldman, S. Medly

Background: Oesophageal carcinoma (esophageal carcinoma) [ONB] is a rare malignant neoplasm arising from the oesophageal epithelium in the nasal vault. It usually takes an aggressive clinical course for which there are no specific treatment guidelines. Pursuing the goals of personalized medicine, we investigated a cohort of recurrent and/or metastatic ONBs using multiparameter molecular profiling approach.

Methods: Formalin-fixed paraffin-embedded tissue samples of twenty (10 male, 10 female patients, age range: 29-84 years) ONBs were profiled at Caris Life Sciences (Phoenix, Arizona, USA) using DNA sequencing (Sanger sequencing, massively parallel sequencing [Illumina NGS], and gene fusion [Archer FusionPlex®]); whole genome RNA microarray (HumanHT-HT-12 v4 beadChip, Illumina), gene copy number assays (chromogenic and fluorescent in situ hybridization) and immunohistochemistry.

Results: Mutations were detected in 41/45 (95.6%) ONBs including TP53 (3 cases), CINNB1 (2 cases), APC, cKIT, MET, and PDGFRA, and Smad4 genes (single cases, respectively). When compared with control tissues, 21 genes were over expressed and 19 genes under expressed by microarray assay (≥1.5x). Some of the upregulated genes included stem cell marker CD24, SCG2 (Secretogranin II) and Insulin-Like Growth Factor Binding Protein 2 (IGFBP-2). None of the cases harbored copy number variations of EGFR, HER2 and MET genes, and no gene fusions were identified. No case expressed PD-L1 (0/6) or IDO 1 (0/3). Multiple protein biomarkers of response or resistance to classic chemotherapy drugs were identified: low EBC1 (capatin sensitivity) in 82% (9/11), high TOP2A (tritocan sensitivity) in 63% (12/19), high TUBB3 (vinristine resistance) in 92% (12/13) and high MRPII (multidrug resistance) in 100% (6/6).

Conclusions: Our study indicates that a subset of ONBs exhibits molecular alterations, notably in the Wnt and cKIT/PDGFRα pathways, that are potentially treatable with novel targeted therapies. Optimization of cytotoxic chemotherapy approaches based on protein expression may be worthy of further investigation.

Legal entity responsible for the study: Caris Life Sciences, Phoenix, Arizona, USA
Funding: Caris Life Sciences, Phoenix, Arizona, USA
Disclosure: Z. Gatalica, A. Ghazalpour, J. Swensen, R. Bender, R. Feldman, S. Medly: Employee of Caris Life Sciences. All other authors have declared no conflicts of interest.

Prognostic relevance of molecular characterization of circulating tumor cells (CTC) in head and neck squamous cell carcinoma (HNSSC)

G. Koutoudes, A. Strati, G. Papatheodoridis, N. Charalambakis, I. Kotsiris, P. Kotelouris, A. Papadopoulos, E. Liannou, A. Psymi

Background: CTCs are considered indicators of residual disease and thus are associated with an increased risk of metastasis. Moreover, hypoxic microenvironment, a major feature of HNSSC, plays a pivotal role in the emergence of CTCs and cancer stem cells. Although rare and exposed to immune mediated destruction, these cells manage to evade the immune system of the host. Therefore, a better understanding of the immunogenicity of these cells and their cross talk with immune cells may shed light to potential immunoimmunotherapy opportunities in HNSSC.

Methods: We quantified by RT-qPCR TWIST1, Stem Cell (SC) markers (CD24, CD44, ALDH1) and PD-L1 in immunomagnetically positively selected CTCs from 90 locally advanced (LA) HNSSC, 33 recurrent/metastatic (R/M) HNSSC and 20 healthy individuals. Patients (pts) with LA disease were treated with cetuximab chemotherapy +/− TPF induction chemotherapy (IC). We assessed the expression of TWIST1, SC markers and PD-L1 at baseline, after completion of IC, at end of chemotherapy and at relapse in pts with LA disease and at baseline in pts with R/M HNSSC. To assess univariate and multivariate analyses of study parameters according to gene expression, chi-square test was used for the categorical clinopathological variables, while patients’ survival curves according to gene expression were generated by Kaplan-Meier analysis and tested for significance using the Mantel-Cox log-rank test.

Results: Pts with PD-L1 positive CTCs at the end of treatment had shorter Progression Free Survival (PFS) (p = 0.001) and Overall Survival (OS) (p = 0.001). Multivariate Cox regression analysis confirmed that PD-L1 overexpression in pts at the end of treatment was an independent prognostic factor for PFS (p = 0.012) and OS (p = 0.009). Expression of CD44 on CTCs at the end of treatment was associated with expression of PD-L1 (p = 0.014).

Conclusions: Liquid biopsies could identify pts at high risk for relapse after adjuvant chemoradiation that may derive benefit from adjuvant therapy in LA disease. PD-L1 expression in CTCs at the end of treatment is a potential biomarker for pt selection for treatment with adjuvant PD1 checkpoint inhibitors.

Legal entity responsible for the study: Attikon University General Hospital, Athens, Greece
Funding: National and Kapodistrian University of Athens
Disclosure: All authors have declared no conflicts of interest.

Mutation profiles of nasopharyngeal carcinomas in South-Eastern European patients


Background: Nasopharyngeal cancer (NPC) is characterized by a remarkable geographical variation and biologic diversity. Importantly, studies investigating mutation profiles of NPC in European populations are scarce. Methods: We investigated the mutational profile of 127 NPC (98% EBV positive) in 93 Greek (GR) and 34 Romanian (RO) patients with locally advanced disease, treated with concurrent chemoradiotherapy (CCRT) or induction chemotherapy (IC) followed by CCRT. In 19 tumors, dissected matched tumor/lymphocyte (T/L) pairs were compared. Mutation (amino acid changing, minor allele frequency <0.1%; splice-site
changing) data were obtained with next generation sequencing (mean depth 3261.5) with a panel targeting areas in 100 NPC, DNA repair, and immune response related genes. Disease-free survival at 3 years (3yDFS) was the clinical endpoint.

**Results:** We identified 1562 mutations in 101/129 tumors (94%). Mutations were mostly found in the cytoplasmic recombination repair (HHR, 4%), chromatin remodelling (1%) and immune response related (IRR, 10%) genes. In the matched T/L samples, common mutations were identified in 10 cases only, the rest harbouring private mutations. Shared T/L mutations occurred at higher frequencies within the same tumor than T- and L-private mutations (p < 0.001). HRR and tyrosine kinase signalling genes, as well as POLE and TP53 carried mostly L-private (p = 0.003). In comparison to OR, patients were younger (p = 0.027), had almost exclusively WHO type II and III tumors (p = 0.025) and presented more often with stage IV disease (p = 0.026), while their tumors had significantly higher mutation load (p < 0.001) and higher numbers of mutations in particular genes, e.g., BRCA1 (p < 0.001). Multivariate analysis revealed BRCA1 mutations (odds ratio [OR] 6.3, 95% CI 1.3-31.4, p = 0.024) and absence of EBV infection (OR: 6.2, 95% CI 1.1-35.9, p = 0.040) as unfavourable prognostic parameters.

**Conclusions:** Different genes and sets of genes are affected in stromal and tumor components of NPC, which is important for targeted treatment considerations. Ethnic differences in mutation profiles exist but do not seem to interfere with patient outcome, which seems adversely affected by the absence of EBV and by the presence of BRCA1 mutations.

**Legal entity responsible for the study:** Hellenic Cooperative Oncology Group

**Funding:** Hellenic Cooperative Oncology Group

**Disclosure:** G. Fountazis: Advisory Board: Astra Zeneca S.A. All other authors have declared no conflicts of interest.

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**Observational study of the cetuximab relative dose intensity (RDI) in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCC): Data on the maintenance and every two weeks use (DIRECT study)**


**Background:** In EXTREME pivotal Phase III trial, Cetuximab (CTx) associated with chemotherapy (CT) based on platinum (cisplatin or carboplatin) + 5-fluorouracil (5-FU), followed by cetuximab single agent (maintenance) has demonstrated improved survival outcomes compared to CT alone in R/M SCC in first-line therapy. DIRECT is the first observational, prospective study evaluating CTx RDI in this setting. Here, we focus on CTx maintenance phase and every two weeks usage (administration frequency at physician discretion).

**Methods:** 157 adult patients with R/M SCC treated in first-line with CTx according to the scheme of the pivotal study in usual medical practice were included in this national multicenter study (56 centers in France over two years (Nov 2012-Jun 2014) and were followed up during a maximum period of 12 months.

**Results:** 45.8% (n = 72) of the patients have received CTx maintenance treatment. The median duration of maintenance was 15.8 ± 10.5 weeks (n = 72). 12-month-PFS rate was 23% (95% CI [14.0%, 33.5%]). 12-month OS rate was 70% (95% CI [57.3%, 79.6%]). For patients with disease free interval less than 6 months (n = 55), 12-month OS rate was 41% (27.1% vs. 54.8%). During maintenance, 54.2% (n = 39) of patients have received CTx every two weeks (e2w) administration and 45.8% (n = 33) once a week. 12-month-PFS rate and 12-month OS rate were not worse in patients with e2w versus weekly administration (weekly, n = 33 vs e2w, n = 39): 18.2% (7.4% 32.8%) vs 27.5% (13.4% 42.3%), p = 0.2, 62.6% (43.6% 76.8%) vs 77% (59.1% 87.8%), p = 0.2 respectively for PFS and OS rates. Cutaneous toxicities (grade ≥ 3) were observed in 21/157 patients (13%). Shared T/L mutations (grade ≥ 3) were similar in the Extreme study.

**Conclusions:** This real life data indicates that CTx maintenance treatment every other week is feasible in R/M SCC patients and seems not to result in a reduced efficacy compared with weekly administration. In addition, cutaneous toxicity rate (grade ≥ 3) was similar in the Extreme study.
Results: Among the first cohort, 125 of 931 cases (13.4%) have post-RT detectable EBV DNA signals but in very low copy number. We observed a significantly higher relapse rate (64.8% vs. 21.3%, P < 0.001) and poor survivals (5-yr OS, 49.5% vs. 85.3%, P < 0.001) in patients with detectable than with undetectable EBV DNA after a median follow-up of 99 months. In the prospective cohort, we classified 441 patients into three subgroups according to blood tests. The subsequent recurrence rates of patients with DNA-negative (n = 362), DNA trace (n = 15), and DNA-positive (n = 64) were 1.4%, 3.3%, and 100%, respectively (P < 0.001). Our analysis of the 426 patients with test results showing negative and positive revealed that the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 92.8%, 100%, 100%, 98.6%, and 98.8%, respectively. The latent intervals from DNA trace to DNA-negative and DNA-positive to verified recurrence ranged from 28-771 days (mean 171) and 0-693 days (mean 119).

Conclusions: NPC patients with post-RT persistently detectable EBV DNA may be regarded as potential existence of "minimal residual disease" and warrant future adjuvant therapy trials. Patients with blood tests showing EBV DNA-positive during follow-up should be regarded as "biomarker failure" and candidates for future trials of early intervention.

Clinical trial identification: CG11133 and CE12111 of the Taichung Veterans General Hospital, Taiwan.

Legal entity responsible for the study: Department of Radiation Oncology, Taichung Veterans General Hospital, Taiwan.

Funding: The Grant from the Ministry of Science and Technology (MOST 103-2313-B-075A-005-M33), Taichung Veterans General Hospital (TCVGH-1027025C, 1071010C, 1047186C), and Bodol’s Trading Co., Ltd., Taiwan.

Disclosure: All authors have declared no conflicts of interest.

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STOP

Triweekly versus weekly cisplatin concurrent with radiotherapy in locally advanced nasopharyngeal carcinoma

M. Lan1, S. Wu1, F. Han1, M. Deng1, C. Chen1, Y. Huang1, Z. Duan2, J. Liao1, L. Tian3, L. Zheng3, T. Lu1

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Background: Comparative studies on triweekly and weekly cisplatin in locally advanced nasopharyngeal carcinoma (NPC) were all based on small sample size, and no definitive conclusion has been established. The aim of this study was to compare the outcomes of concurrent chemoradiotherapy (CCRT) using two different schedules of cisplatin in patients with locally advanced NPC.

Methods: From January 2007 to December 2011, 1582 patients with stage II-IVb NPC, treated with CCRT alone were reviewed. Eight hundred and two patients received triweekly cisplatin (80-100 mg/m² every three weeks, two to three cycles) and 780 patients received weekly cisplatin (30-40 mg/m² every week, over five cycles). Clinical characteristics and treatment factors were well balanced in two groups. Overall survival (OS), disease-free survival (DFS), loco-regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) and acute toxicity profiles were calculated.

Results: Median follow-up time was 64 months (range, 4-194 months). For the entire cohort, the distant metastasis risk was decreased by 26% in the triweekly group than weekly group (hazard ratio [HR] = 0.70, 95% confidence interval [CI] 0.49-0.99). Subgroup analysis revealed that triweekly cisplatin could further improve patients’ 5-year DMFS (92.6% vs. 85.8%, P < 0.001, respectively) and DFS (82.6% vs. 77.6%, P = 0.016, respectively) compared with the weekly group, for patients treated with intensity-modulated radiotherapy (IMRT). Furthermore, the 5-year DMFS rates were significantly improved by using triweekly cisplatin in patients with N3 diseases (HR = 0.37, 95% CI 0.14-0.94) and stage IV diseases (HR = 0.52, 95% CI 0.29-0.93) Grade 3-4 acute toxicities were similar in two groups.

Conclusions: Triweekly cisplatin treatment is more effective than weekly cisplatin regimen in reducing distant metastases in patients with locally advanced NPC, especially for those with N3 or stage IV diseases and who were treated with IMRT.

Legal entity responsible for the study: N/A

Funding: This research was supported by Grants from the National Science Foundation of China (81202124). Disclosure: All authors have declared no conflicts of interest.

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High incidence of cetuximab-related infusion reactions in head and neck cancer pts (real life data)

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Institut Gustave Roussy, Villejuif, France

Background: Cetuximab is crucial in the management of squamous cell carcinoma of the head and neck (SCCHN) patients. Grade 3-4 infusion reactions (IRs) occur in 2% of colorectal cancer (ASPECCT study, ~1000 pts). Despite the 2.7% IR rate in the EXTREME trial (NEJM 2008), higher rates were reported in small series of SCCHN (6-10%). There is an urgent need to better appraise the natural history and the predictive factors for IRs in HNSCC pts exposed to Cetuximab.

Methods: The medical records from all consecutive SCCHN patients (n = 451) treated by cetuximab at Gustave Roussy Cancer Campus Grand Paris) from January 2013 to December 2015 were reviewed. IR severity was defined as per the NCI-CTCAE v4.0. The impact of potential risk factors was analyzed (history of allergy, biological and clinical characteristics that could influence the risk of IR, concomitant drugs, etc) and the patients were enrolled in an observational registry.

Results: All patients analyzed represented a pre-medication including corticosteroids and antihistamines. Of 441 patients, 34 patients (7.5%) presented grade 3-4 IR, nearly all of them requiring intensive care unit referral. Most of the IRs occurred during the first cycle (range: 1-3). The occurrence of grade 3 IR was associated with prior allergy history (P = 0.05) but not with previous radiotherapy or chemotherapy. Further analyses (corticosteroids, concomitant drugs, etc) will be presented during the ESMO 2016 meeting.

Conclusions: In real life, grade 3-4 IR consecutive to cetuximab appears far more common (7.5%) than reported in prospective trials. This is the largest series of patients ever focusing on the risk of IR induced by cetuximab in SCCHN pts. History of prior allergy is a strong predictor of IR and could be used in clinical practice to identify high risk pts and supervise pts. Further prospective data are however required to confirm this.

Legal entity responsible for the study: Gustave Roussy, Université Paris-Saclay, Villejuif, France

Funding: Gustave Roussy, Université Paris-Saclay, Villejuif, France

Disclosure: All authors have declared no conflicts of interest.
Background: Pre-treatment plasma EBV DNA is considered as a prognostic biomarker for NPC patients. Whether the pre-treatment EBV DNA could be a biomarker guiding the treatment for advanced NPC patients warrants investigation.

Methods: TCGO 1303 was a phase III trial comparing induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) versus CCRT alone in stage IV A or IVB NPC patients. In both arms, radiotherapy would be delivered with weekly cisplatin and leucovorin for 3 cycles before the CCRT. The primary endpoint was disease-free survival. Pre-treatment plasma EBV DNA was analyzed.

Results: From September 2003 to August 2009, 479 patients were enrolled. The pre-treatment plasma EBV DNA were collected from 264 patients. The median follow-up was 66 months. The median of plasma EBV DNA was 7862.5 copies/mL. 135 pts were grouped in EBV DNA < 8000 copies/mL (EBV-low) and 129 pts in EBV DNA >= 8000 copies/mL (EBV-high). High plasma EBV DNA was statistically significant with larger tumor size (p < 0.0001), advanced N stage (p = 0.001) and overall stage (p = 0.0002). Between the EBV-low and EBV-high groups, there was no statistically significant difference in DFS (HR = 1.26 (95% CI: 0.85-1.87), p = 0.25) and overall survival (OS) (HR = 1.39 (0.84-2.28), p = 0.20) with Cox proportional hazarded model. Between the IC-CCRT arm and CCRT arm in the EBV-low group or EBV-high group, no significant difference in characteristics was observed between two arms. By univariate Cox regression analysis, there was no statistically significant difference on DFS and OS between IC-CCRT and CCRT in both groups (EBV-high: IC-CCRT vs CCRT: DFS: HR = 0.798 (0.46-1.37), p = 0.40, and OS: HR = 0.85 (0.43-1.69), p = 0.65; EBV-low: IC-CCRT vs CCRT: DFS: HR = 0.73 (0.41-1.28), p = 0.27; and OS: HR = 0.64 (0.32-1.27), p = 0.20).

Conclusions: Pre-treatment plasma EBV DNA cannot be a biomarker of induction MEPEL for stage IVa or IVB NPC patients. The role of pre-treatment plasma EBV DNA should be explored.

Clinical trial identification: NCT00201396

Legal entity responsible for the study: Hsiang-Fong Kao

Funding: National Taiwan University Hospital, Taiwan National Health Research Institutes, Taiwan

Disclosure: All authors have declared no conflicts of interest.

974P Prospective study of cetuximab with cisplatin plus docetaxel followed by concurrent radiotherapy plus cetuximab and cisplatin in patients with chemotherapy-naïve metastatic nasopharyngeal carcinoma

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Background: Metastatic nasopharyngeal carcinoma (mNPC) is generally considered as incurable using conventional therapy. We incorporated cetuximab into the induction therapy and subsequent chemoradiotherapy to treat mNPC in a prospective study.

Methods: Between Jul 2006 to Dec 2014, eligible patients (≥18 years old) with mNPC, including initial metastases (IM) and relapse metastases (RM), entered into the trial according to their willingness. Patients in the study group were treated with docetaxel 75 mg/m2, cisplatin 75 mg/m2, and cetuximab 250 mg/m2 per day, 1, 8, 15, and 22 (initial loading dose of 480 mg/m2), repeated every 3 weeks up to a maximum of 6 cycles, followed by IMRT (68-70 Gy) with concurrent cetuximab 250 mg/m2 weekly for six cycles and cisplatin 75 mg/m2 per three weeks for two cycles, and maintenance cetuximab plus cetozolox for 3 years. Patients in the control group received conventional chemoradiotherapy.

Results: Totally 43 patients in the study group (17 IM and 26 RM patients), and 66 patients in the control group were enrolled. The ORR and CRR after induction chemotherapy were 79.1% and 34.4% for the study group and 47% and 3% for the control group respectively. With a median follow-up of 60 months, 5yOS and 5yPFS were 28.9% and 16.7% in the study group and 10.9% and 0% in the control group, respectively. In the study group the ORR and CRR were higher in the IM than in the RM subgroup (94.1% vs 62%, 52.9% vs 23.1%, both p < 0.05), and IM patients had a longer 5yOS (43.7% vs 19.2%) (p = 0.086). In the study group 13 survivors remained disease-free >36 months, 10 of them were still alive with disease-free survival time ranging from 46 to 92+ months. Five patients (11.6%) had grade 3 cetuximab-related acneiform rash. Occurrence of other most common toxicities were similar between the two groups.

Conclusions: The cetuximab-containing induction and consolidation chemoradiotherapy in patients with chemotherapy-naïve mNPC resulted in excellent long-term disease-free survival and safety, indicating that mNPC is potential curable, especially in patients with initial metastases.

Legal entity responsible for the study: M.C. Merlano

Funding: ARCO foundation

Disclosure: M.C. Merlano. Consultant for Merck Serono. All other authors have declared no conflicts of interest.
Comorbidity and nutritional factors influence on bioradiotherapy (BRT) outcome in head and neck squamous cell carcinoma (HNSCC) patients

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Background: BRT is a validated conservative treatment for patients (pts) with locally advanced HNSCC. Our aim is to analyze the outcome of a large consecutive cohort of pts treated with bioradiotherapy plus cetuximab and to determine disease control and survival related factors.

Methods: 253 pts diagnosed with HNSCC were treated radically with BRT +/- induction chemotherapy (iCT) in our institution (2006-2014). We performed a multivariate analysis (COX) adjusted by classic risk factors, stage, iCT, comorbidity, weight loss (WL), pre-treatment albumin (PTA), albumin drop (AD) and magnesium (Mg). Pts were divided in 3 groups: A1(stage III), A2 (stage IVa-b), B (presence of comorbidity regardless stage). We analyzed complete response rate (CRR), 2-year loco-regional control rate (2yLCR), median progression free survival (mPFS) and median overall survival (mOS) using Kaplan-Meier stratified by iCT.

Results: Median follow up: 60 months (m) (11-115). Overall results: CRR: 76.4 %, 2yLCR:72%, mPFS 31 m (24.7-38.5), mOS 45 m (29-61.7), iCT LogRank 0.0. Group results on table: comorbidity impact on OS in group B was maintained when stratified by stage. Multivariate analysis: comorbidity and stage IV were the main risk factors for mPFS (HR 2.43, p < 0.01), iCT 2.76, p < 0.01 respectively) and OS (HR 2.05, p < 0.01, HR 2.28, p < 0.01 respectively). iCT influenced positively on OS (HR 0.58, p < 0.02). WL and PTA didn’t impact on PFS/OS. AD >10% during treatment was a risk factor for OS (35m vs 85m, HR 2.05, p < 0.01) and on 2yLCR (2.02 and 0.79, p < 0.01 respectively). AD >21% and PTA >3144.8% Mg drop >15% impacted on OS (18.5m vs 85.1m, HR 3.65 p < 0.02).

Conclusions: Comorbidity and stage IV are the main prognostic factors in this group of pts. As iCT impact on survival, comorbidity should be considered when choosing the best treatment. AD at the end of treatment could be a useful prognostic biomarker. Detecting Mg drop and starting supplementation might be essential in pts treated with BRT.

Legal entity responsible for the study: ARCO Foundation
Funding: ARCO Foundation
Disclosure: M. Taberna: Consultant for Merck Serono. All other authors have declared no conflicts of interest.

Table: 977P Groups stratified results

<table>
<thead>
<tr>
<th>Group</th>
<th>CRR (%)</th>
<th>2-year LCR (%)</th>
<th>mPFS (m)</th>
<th>mOS (m)</th>
</tr>
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<tbody>
<tr>
<td>A1</td>
<td>84</td>
<td>95</td>
<td>Not Reached</td>
<td>NR</td>
</tr>
<tr>
<td>A2</td>
<td>72.9</td>
<td>82</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>B</td>
<td>77.7</td>
<td>57.1</td>
<td>17.8 (IC 11.9-22.5, p &lt; 0.001)</td>
<td>32 (IC 25.4-40.3, p = 0.004)</td>
</tr>
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</table>

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Does post-induction chemotherapy PET/CT response predict outcome in young adult nasopharyngeal carcinoma? Prospective study from CCHE

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Background: This is a prospective study aiming to evaluate the predictive value of [18F]fluorodeoxyglucose positron emission tomography ([18F]FDG PET/CT), reflected in terms of disease-free survival (DFS) and overall survival (OS), in pediatric patients who had received post induction chemotherapy for locally advanced nasopharyngeal carcinoma (LANPC). Pediatric patients were treated definitively with 3 courses of induction platinum-based chemotherapy followed by concurrent chemoradiation (CRT) with simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT).

Conclusions: This is a prospective study included LANPC (stage II-III) pediatric patients treated definitively and consecutively between January 2008 and December 2014 with induction chemotherapy; cisplatin, and 5-fluorouracil (5FU) followed by SIB-IMRT to a total dose 61.2Gy utilizing weekly cisplatin. The volume of radiotherapy was
based on tumor response to Induction chemotherapy. All patients had baseline pretreatment and post induction chemotherapy 18F-FDG PET/CT. Metabolic response of the primary tumor and LN was assessed using maximum standardized uptake value (SUVmax) that was correlated with treatment outcomes, OS and EFS.

**Results:** The study included 36 eligible pediatric LANC patients. The 3-year OS and DFS rates were 84.6 % and 79.5 %, respectively. The median OS and EFS intervals were not reached. On a univariate analysis, the 3-years OS and EFS were significantly higher in patients with post induction metabolic regression of SUV max >65% for the primary and 57% for the nodal metastases (P = 0.02). Furthermore, OS and EFS were lower in patients with initial high nodal metabolic activity (P = 0.004) and (P = 0.005) with SUV max cutoff values (14.5) and (6.9) respectively. Also Initial SUV-LN > SUV-Primary showed significant lower OS (P = 0.004) and EFS (P = 0.005).

**Conclusions:** In this study, the degree of metabolic regression in post-induction chemotherapy 18F-FDG PET/CT was a potential independent prognostic indicator for clinical outcomes in LANC pediatric patients (treated definitively with PF induction chemotherapy followed by CRT). Further controlled clinical trials are worthwhile.

**Legal entity responsible for the study:** CCHE

**Funding:** CCHE

**Disclosure:** All authors have declared no conflicts of interest.
haematological (8.9%), gastrointestinal (3.6%) and feverish (3.6%) and hemorrhagic (1.8%) events. The median cost of the whole drug treatment was 51.65 USD (1 USD = 7.8 HKD).

Conclusions: Oral cyclophosphamide is an acceptable 3rd line or subsequent line systemic therapy for loco-regionaly advanced recurrent or metastatic NPC with acceptable toxicity and limited financial burden to patients.

Legal entity responsible for the study: Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

85SP

An advanced tumor shape radiomic signature predicts recurrence of locally advanced (LA) HNSCC patients (pts)

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Background: Radiomics delivers multifaceted tumor characterization with complex quantitative features extraction from medical imaging related with prognostic clinical outcomes in cancer decision support. Distinct from texture and histogram analysis, advanced 2D and 3D shape parameters could reflect tumor local invasion and outcome as well as histological invasion patterns in LA HNSCC pts.

Methods: Tumor contours were defined from semi-automatic delineation of baseline contrast-enhanced CT scan. We trained a radiomic signature made of 27 complex parameters reflecting tumor convolution and shape complexity from 120 LA HNSCC pts retrospectively evaluated at Gustave Roussy Institute. We validated this particular shape signature on 86 LA HNSCC pts from TCGA database with assessable pre-treatment CT. Theses 3D silhouette parameters (n = 27) comprised fraction of convex on concave edges, distance to arithmetic mean average position, and Minkowski dimension. We connected it to PFS, OS, and outcome events. Concordance Index (CI) and Kaplan Meier estimations assessed our signature's competence. Unsupervised bi-clustering methods linked radiomics features and clinical endpoints.

Results: We successively trained a powerful shape signature based on 9 complex parameters in these populations, significant through OS, PFS and local control predictions. Combining our shape radiomic signature with clinical factors (age, tumor location, ...) significantly improved results over clinical evaluation alone. Particularly, an unsupervised analysis of radiomics shape factors alone linked with tumor location (p < 0.05) independently of tumor volume, translating histological invasive traits through radiomics analysis.

Conclusions: We created a shape-based radiomic signature presenting a potential prediction of invasive histological characters, correlated recurrence and prognosis in LA HNSCC pts, independently from TNM stage, tumor location, surgery, chemoradiation or further treatment, which could change the initial treatment plan for LA HNSCC pts and improve patient stratification.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

85SP

Utility of algorithm-based chemoradioselection for advanced laryngeal and hypopharyngeal carcinoma

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Background: At our institute, a “chemoradioselection” strategy has been used to select patients with head and neck cancer for organ preservation. In brief, tumor responses are evaluated at 40 Gy of concurrent chemoradiotherapy (CRT). Responders (i.e., chemoradiosuccess, CRS) receive further CRT up to 70 Gy, while non-responders (N-CRS) are recommended to undergo radical surgery (N-CRS-op). To those who refuse surgery (N-CRS-refu), continuous CRT is administered. In this study, the results of advanced laryngeal and hypopharyngeal carcinomas were examined.

Methods: From 2000 to 2012, 123 patients with stage III (44), IV (79) larynx (64) and hypopharynx (59) excluding T4 cases were enrolled to this algorithm-based treatment. Split (15mg/m2 x 5 days, 2000-2000Gy) or bolus (80mg/m2, 30Gy of CRT, respectively.

Results: Based on the algorithm, 64 patients were CRS. The remaining 59 N-CRS patients proceeded to either N-CRS-op (34) or N-CRS-refu (25) arm. The 5-yr OS and DSS were 67% and 77%, respectively. The 5-yr OS of N-CRS-refu (47%) was significantly (p = 0.0193) lower than that of CRS (73%) or N-CRS-op (70%).

Conclusions: Algorithm-based chemoradioselection might provide a novel platform for the treatment of advanced head and neck cancer, taking full advantages of CRT and radical surgery, and thereby achieving optimization of the treatment intensity.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

85SP

Pazopanib in patients with progressive recurrent or metastatic (R/M) salivary gland carcinoma (SGC): Further evaluation of efficacy including tumor growth rates (GR) analysis. H & N Unicancer Group PACSA trial with the NEFCOR

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Background: The excision repair cross-complement group 1 (ERCC1) expression is related to prognosis and sensitivity to platinum-based chemotherapy in various cancers, especially lung. Platinum is the most frequently chemotherapeutic used in treatment of squamous cell carcinoma of the head and neck (SCCHN), and ERCC1 has been used as a predictive biomarker of cisplatin-containing chemo or chemo-radiotherapy. In this study, we assessed the prognostic role of ERCC1 protein expression in surgically resected SCCHN.

Methods: Between 1994 and 2012, 204 patients who were diagnosed with oropharynx or oral cavity cancer and underwent curative surgical resection were included. ERCC1 protein expression was evaluated by immunohistochemistry. Clinical and pathologic records were retrospectively reviewed.

Results: ERCC1 protein was positive in 136 (66.7%) patients. High ERCC1 expression was associated with oral cavity cancer (P = 0.011), well differentiated tumor (P = 0.036), and HPV negativity (P = 0.001). High ERCC1 expression showed trend toward poor prognosis but not statistically significant (P = 0.137 for PFS, P = 0.332 for OS). The prognostic role of ERCC1 was not different according to the HPV status or following chemo or radiotherapy. However, patients with high ERCC1 showed poor prognosis in advanced TNM stage (HI/IV), but no difference in early stage (I/II).

Conclusions: ERCC1 protein expression can help to predict prognosis in surgically resected oropharynx or oral cavity SCCHN, especially in advanced stage.

Legal entity responsible for the study: N/A

Funding: The Catholic University of Korea

Disclosure: All authors have declared no conflicts of interest.
phase II trial to assess Pb efficacy in SGCHN, and present here results of the ancillary GR study.

**Methods:** Pts with confirmed progressive R/M SGCHN received Pb 800 mg daily until progression (PD). Primary endpoint was 6-mo PFS rate, with unacceptable and promising rates of 20% and 40%. Tumor volumes were measured in a medical imaging workstation (Advantage Workstation, GE Healthcare) Assuming exponential growth, GR was defined as \( \log_{10}(V_t/V_0)/dt \), where \( V_0 \) and \( V_t \) are tumour volumes at time 0 and t and \( dt \) the time in months between time 0 and t. Two time periods: pretrial period, from 3-6 mo before inclusion to inclusion (GRpre) and trial period, from inclusion to 3 mo later (GRpost). GR variation was defined as the difference \( GR_{\text{post}} - GR_{\text{pre}} \), a negative difference means a GR break (\( GR_{\text{post}} < GR_{\text{pre}} \)). A GR variation \( < 0 \) means a tumor volume decrease.

**Results:** From 2013 to 2015, 72 pts were enrolled: 49 ACC and 20 non-ACC (3 ineligible excluded). M:F = 32:37, median age 59 yrs (range 27-84). Pb 0-1 = 42:27. Pb tolerance was as expected. Among 63 pts (45 ACC, 18 non-ACC) evaluable for efficacy (6 non progressive excluded), 6-mo PFS rate was 47% (95%CI:36-60) with 30 pts without PD at 6 mo, median PFS was 5.9 mo. Median OS was 17 mo. The 6-mo PFS met the criteria for efficacy conclusions of the trial: GR study was performed among 31 patients (24 ACC, 7 non-ACC). 6-mo PFS was 61% [IC95%:43;76] with 19 pts without progression after 6 mo. Median PFS was 8.2 mo. GR variation analysis showed a significant GR break 3 mo after Pb start (median -0.37; p=0.001) with 26 pts (48% [IC95%:66;95]) having a GR break. 15 pts (48% [IC90%:30;67]) had a volume decrease after Pb start. GRpre and GR variation were not associated with PD at 6 mo.

**Conclusions:** There is a significant decrease in GR between evaluations done before inclusion and 3 months after Pb start, i.e. a break in tumor growth rate, in agreement with the PFS based conclusion of promising efficacy of Pb in R/M SGCHN.

**Clinical trial identification:** NCT02398320

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**Relationships between imaging characteristics and hearing levels in patients with vestibular schwannomas treated by stereotactic radiosurgery**

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**Background:** This study aimed to investigate the correlation between the imaging characteristics and audiological features in patients with vestibular schwannomas and to analyze hearing outcomes following stereotactic radiosurgery.

**Methods:** This was a retrospective study of 100 patients who underwent stereotactic radiosurgery for vestibular schwannomas between January 2002 and January 2012. The demographic data, clinical presentation, imaging characteristics, pure-tone audiogram, speech discrimination, stapedial reflex, auditory brainstem response, oculomotor control, caloric test, and hearing outcome following radiosurgery were reviewed. Imaging characteristics, including tumor size and location, fundus involvement, brainstem compression, and intracanalicular (IAC) dilatation, were analyzed.

**Results:** Tumors were classified by their location as extracanalicular (8%), intracanalicular (19%), and intracanalicular and extracanalicular (73%). Tumors may be localized, without occupying the fundus of the IAC (63%), or they may extend to the fundus (37%). Dilatation of IAC was noted in 82 cases (82%). The tumors were in contact with the brainstem in 15 cases (15%); the brainstem was compressed by the tumors in 45 cases (45%). Abnormalities in the stapedial reflex, oculomotor control, and caloric tests were not significantly associated with tumor size. Tumor size was positively correlated with the pure-tone average (PTA; \( p = 0.005 \)).

**Conclusions:** Imaging characteristics, including fundus involvement and tumor size, are correlated with the PTA before radiosurgery and are not associated with hearing preservation following radiosurgery. An accelerated rate of hearing loss was observed in the first 3 years after radiosurgery was performed.

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**Ototoxicity in locally advanced head and neck cancer (LAHNC) patients (pts) treated with induction chemotherapy (IC) followed by cisplatin-based chemoradiotherapy (CRT)**

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3 Medical Oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands.
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5 Radioterapy, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands

**Background:** The CONDOM study; a randomized phase II trial, investigated feasibility of docetaxel/cisplatin/5-fluouracil (TPF) followed by conventional radiotherapy with cisplatin 100 mg/m² on days 1, 22, 43 (cis100 + RT) versus accelerated radiotherapy with cisplatin weekly 40 mg/m² (cis40 + ART) in LAHNC pts. The effect of the two regimens on ototoxicity was investigated.

**Methods:** Audiometry was carried out at baseline, during and after TPF before start of CRT, and 1, 4, 8, and 12 months after end of treatment. Air-conduction thresholds were determined in octave steps from 1 kHz until 8 kHz. Where 1 to 4 kHz is relevant for speech. Based on baseline thresholds we divided the pts in two groups; pts with baseline thresholds ≤ 50 dB and > 50 dB.

**Results:** 62 pts started with TPF; 56 pts were randomized to cis100 + RT (n = 27) or cis40 + ART (n = 29). Compliance to audiometry was low, mostly due to poor physical condition. Pts included in this analysis were 12 in cis100 + RT and 11 in cis40 + ART. Mean cumulative cisplatin dose was 498 mg/m² (SD 66.1) for cis100 + RT and 490 mg/m² (SD 55.8) for cis40 + ART (p = 0.75). Hearing deterioration over time was gradually for cis40 + ART and abrupt for cis100 + RT with a wide spread in both groups. Mostly, the abrupt hearing deterioration occurred during CRT. Hearing loss was most prominent at 8 kHz and almost absent at 2 kHz. We used the Wilcoxon test for our hypothesis that pts treated with cis100 + RT suffer more hearing loss than pts treated with cis40 + ART, showing a difference for 8 kHz (z = 2.07; p = 0.039) and 4 kHz.
Table: 986P

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Cis100 + RT</th>
<th>Cis40 + ART</th>
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<tr>
<td>8 kHz</td>
<td>41 dB</td>
<td>20 dB</td>
</tr>
<tr>
<td>4 kHz</td>
<td>30 dB</td>
<td>12 dB</td>
</tr>
<tr>
<td>2 kHz</td>
<td>7 dB</td>
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</table>

Conclusions: After TPF CRT with cis40 + ART is less ototoxic than CRT with cis100 + RT.

Clinical trial identification: NCT00774319

Legal entity responsible for the study: Carla van Herpen

Funding: Sanofi Aventis Netherlands Dutch Cancer Society

Disclosure: All authors have declared no conflicts of interest.

Comparison of the toxicity and response of a novel outpatient weekly CDFLEM (cisplatin, docetaxel, fluorouracil, leucovorin, epirubicin, methotrexate) induction chemotherapy versus triweekly TPF or PF in locally advanced SCCHN

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Background: Triweekly TPF and PF induction chemotherapy (IndCT) are the most popular and effective regimen for locally advanced squamous cell carcinoma of the head and neck (SCCHN). However, significant ethnic differences in susceptibility to the effects and toxicities exist. We designed a novel weekly CDFLEM IndCT and compared treatment outcome with TPF/PF from literature in locally advanced SCCHN.

Methods: A four-drug regimen (C-D-F-E-L-M) consisting of (1) cisplatin 60 mg/m², day 1, (2) docetaxel 50 mg/m², day 6, (3) 5-fluorouracil 2500 mg/m² + leucovorin 250 mg/m², day 15, (4) epirubicin 30 mg/m² + methotrexate 30 mg/m², day 22, were alternatively delivered once per week, 4 weeks per cycle. From September 2011 to December 2013, 78 patients with stage III/IV SCCHN received 3-4 cycles IndCT of CDFLEM, followed by local therapy (including surgery, radiotherapy, concurrent chemoradiotherapy, or bio-radiotherapy).

Results: Baseline characteristics of 78 patients are as follows: primary of oral cavity/oropharynx/hypopharynx/larynx = 23/26/24/5; stage III/IV = 16/62; median age = 51 (range 33-77); male/female = 73/5; performance status ECOG 0-1/2 = 75/3. Synchronous second or triple primary tumors were also noted in 10 patients. We obtained an overall response rate of 97.3% (CR 39.2% + PR 58.1%) for 74 evaluable patients. The Overall response rate in the TAX-323 trial was 53.6% (CR 6.6% + PR 47.0%) for the PF and 67.8% (CR 8.5% + PR 59.3%) for the TPF regimens, respectively. The corresponding figures in the TAX-324 trial was 64% (CR 15% + PR 49%) vs 72% (CR 17% + PR 55%), respectively. Gr 3/4 mucositis/neutropenia were observed in 77% for our weekly CDFLEM, 11% and 4.6% for PF and TPF in the TAX-323, 27% and 22% for PF and TPF in the TAX-324. Gr 3/4 leukopenia was 38.4% for our CDFLEM, 22.9% and 41.6% for PF and TPF in the TAX-323, 56% and 83% for PF and TPF in the TAX-324.

Conclusions: IndCT with our weekly CDFLEM regimen has a higher response rate and a lower Gr 3/4 mucositis/neutropenia than triweekly PF/TPF in patients with locally advanced SCCHN.

Clinical trial identification: JF11153A of the Taichung Veterans General Hospital

Legal entity responsible for the study: Department of Radiation Oncology, Taichung Veterans General Hospital, Taiwan

Funding: None. Taiwan branch

Disclosure: All authors have declared no conflicts of interest.

Retrospective study of weekly paclitaxel-cetuximab (WPC) in unselected patients (p) with recurrent/metastatic head and neck squamous cell carcinoma (RM-SCCHN)

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Background: WPC is an active treatment in RM-SCCHN, specially for unfit p not candidates to platinum. There are limited data so far about prognostic factors (PFs) in real-life practice.

Methods: Outcome data (Response and survival) along with PFs analysis of RM-SCCHN p treated in our centre with weekly paclitaxel (80 mg/m²) and Cetuximab (400/250 mg/m²) were retrospectively reviewed.

Results: 148p were treated with WPC between January 2008 and July 2014. Female 15p (10.3%) Median age 62 years (38-87). Location: larynx 44p (29.7%), oral cavity 44p (29.7%), oropharynx 26p (17.6%), hypopharynx 11p (7.4%) and other 25p (15.6%).

Previous platinum-based therapy: 103p (69.6%) as initial treatment for localized stage, 31p (20.3%) for recurrent/metastatic disease. Stage: 101p (68.2%) unresectable advanced disease, 9p (6.1%) metastatic disease and 38p (25.7%) both.

Median number cycles: 9(1-27). 64p (43.2%) received cetuximab maintenance. Response rate (RR): 70p (47.3%) objective response (OR) (complete + partial), 30p (20.3%) stable disease (SD), 48p (32.4%) progressive disease (PD). Median overall survival (OS) was 10 months (95%CI:3.11-11.69) and progression free survival (PFS) was 7 months (95%CI:8.88-12). Analyzed PFs Age, Sex, ECOG, Comorbidity index (CI)(ACE27 and Charslton CI), location, RR, stage, and albumin (A1), hemoglobin(Hb) and magnesium(Mg) serum levels were analyzed at baseline and monthly during therapy until PD or death. BSalud level <3 gr/dL and Hb decrease were prognostic of SLP in univariate analyses (UA), but only PD showed worse independent FP in Cox multivariate analysis (MA).

Significative factors in UA for OS were: PD, ACE 27 >1, Charlson CI >3, ECOG >1, previous disease free interval ≤20 m, Al basal level <3 gr/dl, Hb and Mg decrease: In MA, both PD and a 10% or less decrease in serum Mg levels were the only independent PFs for poor OS.

Conclusions: OS and PFS of a non-selected population of RM-SCCHN p treated with WPC was similar to that reported in a previous phase II trial, and comparable to platinum based treatment. Decrease of Mg levels during WPC therapy might be a prognostic biomarker that could be tested in prospective trials.

Legal entity responsible for the study: Isabel Pajares Bernad

Funding: Department of Medical Oncology. Miguel Servet University Hospital

Disclosure: All authors have declared no conflicts of interest.

Clinical-dosimetric analysis of factors predisposing to chronic dysphagia measured using CTCAE criteria among locally advanced oropharyngeal cancer patients treated definitively by intensity modulated radiotherapy with concurrent chemotherapy

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Background: Concurrent chemoradiotherapy in oropharyngeal cancers results in anatomical changes to the pharyngeal constrictors (PCM), larynx and parotid glands leading to chronic dysphagia. This study was done in to find out the incidence of chronic dysphagia after CRT and analyse its correlation with patient clinical factors and specific dose volume parameters of PCM, larynx, oral cavity and parotid glands in locally advanced oropharyngeal cancer patients undergoing concurrent chemoradiotherapy.

Methods: 52 patients with KPS ≥70 of stage III-IVA oropharyngeal cancers were enrolled and treated with concurrent chemoradiotherapy between 2012-2014 with IMRT dose of 66 Gy in 30 fractions and 5 cycles of weekly cisplatin 40 mg/m². Patient clinical factors and Doses to the PCM, larynx, oral cavity and parotid glands such as Mean dose, V10 and V20 were measured from dose volume histograms. Clinical dysphagia was measured at baseline and after 6 months of completing CRT using CTCAE v4.03. These factors were analysed for their correlation with the severity of post CRT chronic dysphagia.

Results: It was found that the clinical factors such as pretreatment dysphagia, nodal stage, TNM stage, tumour volume and mucositis grade at CRT completion had a significant correlation with post CRT chronic dysphagia. On applying spearman’s correlation coefficient for dosimetric factors it was found that the Mean dose, V10 and V20 of PCM, larynx and the mean dose of parotid gland and oral cavity had a positive significant correlation with the severity of post CRT chronic dysphagia. On ANOVA
Cetuximab in combination with platinum-based chemotherapy or radiotherapy in recurrent and/or metastatic SCCHN in a non-selected patient cohort (Interim analysis of the phase IV SOCCER trial)

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Background: Cetuximab in combination with platinum-based chemotherapy followed by cetuximab monotherapy until progression significantly prolonged overall survival (OS) in patients with recurrent and/or metastatic squamous-cell carcinoma of the head and neck (SCCHN) (EXTREME trial). SOCCER is a prospective, non-interventional study to evaluate symptom control in patients with recurrent and/or metastatic SCCHN treated with Cetuximab in combination with platinum-based chemotherapy or radiotherapy.

Methods: 239 patients with recurrent and/or metastatic SCCHN were enrolled. Full information on the concomitant therapy were available for 196 patients. Response rates for the different Cetuximab containing therapy regimens as well as reasons for treatment discontinuations were evaluated.

Results: 82 and 76 patients received Cisplatin or Carboplatin + Cetuximab, respectively, and 38 patients were treated with RT + Cetuximab for recurrent disease. Compared to the EXTREME trial, this study included more patients with metastatic disease (62% vs 47%) and more patients with an ECOG score of ≥2 (23% vs 12%). Median treatment duration of Cetuximab was 4.8 weeks in combination with radiotherapy and 11 weeks in combination with chemotherapy: Main reasons for Cetuximab treatment discontinuation was tumor progression (48%), death (14%) and patients wish (12%). Treatment was discontinued due to toxicities in 7% of the patients. Response data were available in 103 patients. The overall response rate (ORR) and the disease control rate (DCR) were 50 / 76% in the radiotherapy group, 43 / 76% in the Cisplatin group and 31 / 71% in the Carboplatin group, respectively. The median OS of 8.8 months and the median progression free survival of 5.0 months (both preliminary results) are comparable to the results in the phase III EXTREME Trial.

Conclusions: The interim analysis of the SOCCER trial (non-selected patient cohort) is in agreement with the published efficacy and safety data of Cetuximab in combination with platinum-based chemotherapy in first line treatment of recurrent and/or metastatic SCCHN. 1 Vermarkten JB et al., N Engl J Med 2008, 359: 1116-1127.

Clinical trial identification: EMR062202-542

Legal entity responsible for the study: Merck Serono, Universitätsklinikum Erlangen

Funding: Merck Serono
tyrosine kinase activity. The purpose of the research was to study the EGF/sEGFR ratio in tumor tissue and blood of patients with HNC depending on tumor response to the therapy with anti-EGFR MA - Cetuximab (C).

Methods: Levels of EGF and sEGFR and their ratio were studied by ELISA in tumor tissue and blood of 20 patients with HNC squamous cell carcinoma. C- 400 mg/m2 was administered on day 1 and 250 mg/m2 weekly, combined with cisplatin 100mg/m2 on day 1, fluorouracil 100mg/m2 - 96-hour continuous iv infusion q3w. The blood of 20 healthy donors was used as the control.

Results: EGF/sEGFR ratio in the blood of pts before the treatment was various and influenced on the tumor response: in 17 pts with complete and partial response (CR + PR) it was 30% lower than in 13 patients with stabilization (S) and progression (P). Compared to the donors, the ratio was 12.6 and 16 times higher in pts with CR + PR and S + P correspondingly. After the therapy the EGF/sEGFR was 2.5 times lower in pts with CR + PR than in pts with S + P but exceeded the normal level by 4.6 times. The ratio was still 11.5 times higher in pts with S + P than in the donors. The data aquired from the tumor tissue were similar: EGF/sEGFR level in pts with CR + PR was 2.8 times lower than in those with S + P.

Conclusions: EGF/sEGFR ratio is supposed to be a specific biological index for the EGFR cascade in the tumor tissue and in the blood reflects the tumor response for anti-EGFR MA - C et in pts with HNC.

Legal entity responsible for the study: Rostov Research Institute of Oncology

Funding: Ministry of Health of the Russian Federation

Disclosure: All authors have declared no conflicts of interest.

**SNP1**

**Genetic polymorphisms in DNA mismatch repair-related genes predict outcome in patients with head and neck squamous cell carcinoma treated with cisplatin and radiotherapy**


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Background: Cisplatin (CDDP) associated with radiotherapy (RT) has been used in patients with HNSCC treated with CDDP and RT.

Methods: DNA of 90 consecutive HNSCC patients treated with cisplatin and RT was analyzed for the following potential DNA repair gene polymorphisms: MSH3 c.3133GG, MSH2 c.211T > C, MSH2 c.3131GG > A, EXO1 c.1765GA or AA, EXO1 c.2270C > T single nucleotide polymorphisms (SNPs) of the mismatch repair (MMR) pathway, after the outcome of 90 consecutive HNSCC patients treated with CDRT and RT.

Results: Carriers of the genotypes were under a 2.31-fold increased risk overall HNSCC than others. Among smokers, FASL TT genotype was more frequent in overall HNSCC patients (27.9% vs 16.2%, P= 0.001) and in those with SCC of oral cavity (30.0% vs 16.2%, P= 0.006), pharynx (29.9% vs 16.2%, P= 0.007), and larynx (25.4% vs 16.2%, P= 0.03) than in controls. Carriers of the genotypes were under a 2.4, 5.6, 2.93 and 2.54-fold increased risks of overall HNSCC and SCC of the mentioned subsites than others, respectively. An excess of FASL CT or TT plus FAS AA or AG combined genotype was seen in overall HNSCC patients compared to controls (91.3% vs 84.5%, P< 0.001). Carriers of the genotype were under a 2.31-fold increased risk overall HNSCC than others. Among smokers, FASL TT and FAS AA genotypes were associated with 165.8% and 81.05-fold increased risks of HNSCC (P< 0.001), respectively. FASL c.-844C > T, FAS c.671A > G SNPs and tobacco was the best interaction MDR model for risk of overall HNSCC and SCC of oral cavity, pharynx and larynx (P< 0.001). The median follow-up time of HNSCC patients was 46.0 months (1.6-166.0); no association of SNPs and patients survival was seen in study.

Conclusions: Our data present preliminary evidence that inherited abnormalities in MSH3 c.3133GG genotype and GG or GA genotype were under a 2.31-fold and 10.29-fold increased risks of presenting moderate or severe neoprotectivity and ototoxicity after chemoradiation than others, respectively. The EXO1 c.1765GA or AA genotype contributed to patients 9.55 more chances of achieving partial (PR) or stable disease (SD) than others. Patients with the EXO1 c.2270C > T genotype were under a 4.69-fold and a 4.03-fold increased risks of presenting moderate or severe neoprotectivity and none or mild ototoxicity after chemoradiation than others. The GT and AC haplotypes of EXO1 c.1765G > A and c.2270C > T SNPs were associated with a 9.11 and 4.00-fold increased risks of none or mild neoprotectivity and moderate or severe ototoxicity, and a 9.55-fold increased risk of achieving PR or SD than others, respectively.

Conclusions: Our data present, for the first time, preliminary evidence that inherited abnormalities in MMR pathway, related to MSH3 c.3131GG > A, EXO1 c.1765G > A and EXO1 c.2270C > T SNPs, may change rate of complete response and side effects in patients with HNSCC treated with CDRT and RT.

Legal entity responsible for the study: University of Campinas

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

**SNP2**

**An optimal cumulative dose of cisplatin in chemoradiotherapy as a definitive treatment for non-metastatic nasopharyngeal carcinoma: a retrospective multicenter study**


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Background: To date, there is no recommended optimal cumulative dose (OCD) of cisplatin in definitive chemoradiotherapy (CRT) for non-metastatic nasopharyngeal carcinoma (NPC). We conducted a retrospective study to determine a MCCD in NPC treated with CRT.

Methods: Histologically confirmed non-metastatic NPC patients treated at the Ramathibodi and Siriraj Hospitals between 2007 and 2015 were included. Baseline patient characteristics, treatment modality and survival were abstracted. The OCD of cisplatin >200 mg/m2 was used as a stratification dose level. Primary end point was 3-year survival (OS). The Kaplan-Meier with log-rank test was used for analysis. A p-value <0.05 was used to indicate statistical significance. All statistical tests were two sided.

Results: Total of 289 NPC patients were included for analysis. Two hundred and thirty one patients received OCD of cisplatin >200 mg/m2, while 58 patients did not. Median age was 52 (range 17-75). Median radiation dose was 4960 GY (range 1440-7840). Median cisplatin dose was 240 mg/m2 (range 75-361). There was no statistical difference in demographics between these 2 groups, except radiation interruption was less in OCD of cisplatin >200 mg/m2 (72% vs 3%, p < 0.001). Median follow up time was 30.5 months. 1 year OS was similar between both groups (48.9 vs 48.3 months, p = 0.256). 3-year disease free survival (DFS) was not different (45.4% vs 37.9%, p = 0.322).

Conclusions: Our study demonstrated no significant difference in 3 year OS and DFS between OCD of cisplatin greater or lesser than 200 mg/m2. A prospective study...
Comparing standard vs lower dose of cisplatin is warranted to minimize cisplatin related toxicity during chemoradiotherapy for NPC.

**Legal entity responsible for the study:** N/A

**Funding:** N/A

**Disclosure:** All authors have declared no conflicts of interest.

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**Background:** HNSCC pts often need a PEG during their disease. While PEG is studied in depth for locally advanced disease, this is not the case for r/mHNSCC, where therapeutic PEG it supposed to compensate for impaired swallowing, aspiration and to improve the patient’s nutrition status with a potential positive effect on outcome.

**Methods:** We retrospectively analyzed patients with r/mHNSCC referred for palliative systemic treatment between 2005 and 2015. Patients, disease and treatment characteristics were assessed, including the presence of PEG at the start of 1st-line systemic treatment. The Kaplan-Meier method and multivariate Cox regression models were performed to assess the association between survival and PEG status. The log-rank test was used to compare survival between groups.

**Results:** We included 110 pts in our analysis. 100pts received first-line therapy. Forty-two patients (42%) had a PEG at the time of palliative treatment. The median survival was 8 months (95% CI, 6.5-12.0months). ECOG PS was the strongest prognostic factor in our cohort (HR = 2.55, p < 0.001). Overall survival was 4.5months (95% CI, 6.1-11.7months) for pts with PEG and 11.5months (95% CI, 10.9-16.9months) without PEG (adjusted HR = 2.55, p < 0.001). Survival from first occurrence of distant metastases was significantly lower in PEG carriers as compared to patients without a PEG (7.5 vs 15.5 months, adjusted HR = 2.60, P < 0.001).

**Conclusions:** The presence of PEG feeding tubes in patients with r/mHNSCC is an independent negative prognostic factor. Currently applied prognostic factors could be insufficient for an adequate adjusted multivariate analysis in r/mHNSCC. Presence of placement of PEG does not seem to prolong survival in this advanced patient population. This data is hypothesis generating. The impact can be important and outweigh other survival benefits due to systemic therapy.

**Legal entity responsible for the study:** Cantonal Hospital St. Gallen

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**Disclosure:** All authors have declared no conflicts of interest.

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**Background:** We focused on Calreticulin (CALR) on the basis of proteomic differential display analysis using data from 111 patients with OSCC. The association between CALR expression and clinicopathological characteristics, and patient survival were analyzed.

**Methods:** CALR expression was investigated by immunohistochemistry in tissue samples from 111 patients with OSCC. The association between CALR expression and clinicopathological characteristics, and patient survival were analyzed.

**Results:** Immunohistochemical staining of CALR was observed in the cytoplasm of the cancer cells. Among 111 OSCC patients, high expression of CALR was observed in 44 patients (39.6%), whereas 67 patients (60.4%) showed low expression of CALR. Significant association was found between CALR expression and T classification (p = 0.0027), N classification (p = 0.0219), stage (p = 0.0013), and patient outcome (p = 0.0014). The 3-year survival rates of patients with CALR high- and low-expression tumors were 50.1% and 86.6% respectively, which was significantly different (p = 0.0001) as estimated by log-rank test. Multivariate analysis revealed that the reduced term survival was correlated to high levels of CALR expression (p = 0.0001).

**Conclusions:** These results suggest that elevated expression of CALR might play an important role in the progression of OSCC and could be considered as a useful prognostic factor in patients with OSCC.

**Legal entity responsible for the study:** Yamaguchi University Graduate School of Medicine

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**Disclosure:** All authors have declared no conflicts of interest.
Results: Between April 2015 and January 2016, 10 pts (median age: 62.5 years; site location: larynx (2), hypopharynx (2), oropharynx (2), oral cavity (4)) were enrolled, including 6 pts previously treated with cetuximab. No dose limiting toxicities (DLT) were observed at the first dose level. At the second dose level, 1 pt presented rapid disease progression and was therefore replaced as he could not be evaluated for toxicity. One pt out of 6 experienced DLT (Grade 4 thrombopenia lasting more than 7 days). The most common grade 3/4 treatment-related adverse events were neutropenia (n = 2), anemia (n = 2), hypophosphatemia (n = 2), hypokalemia (n = 2), hypomagnesemia (n = 1) and hypoglycemia (n = 1). No objective responses were observed but 4 pts achieved a stable disease according to RECIST v1.1, including 2 pts previously treated with cetuximab.

Conclusions: The MTD of ribociclib in combination with standard dose of cetuximab is 600mg daily (3 weeks on/1 week off). An expansion cohort is currently ongoing.

Clinical trial identification: EudraCT 2014-005371-83

Legal entity responsible for the study: Cliniques universitaires Saint Luc, Brussel, Belgium

Funding: Novartis company

Disclosure: All authors have declared no conflicts of interest.

1003P A comparison of cetuximab-containing regimens for recurrent/metastatic squamous cell head and neck carcinoma: the clinical significance of weekly paclitaxel and cetuximab


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Background: The combination chemotherapy of weekly paclitaxel and cetuximab has been a treatment option for recurrent/metastatic squamous cell carcinoma of head and neck (R/M SCCHN), however, the effectiveness of the regimen has not yet been compared with the current standard regimen, EXTREME (combination of 5-FU, cisplatin and cetuximab).

Methods: We retrospectively reviewed the clinical records of R/M SCCHN patients who received cetuximab-containing chemotherapy as 1st line; of them, patients receiving weekly paclitaxel and cetuximab regimen (cohort A) and the EXTREME regimen (cohort B) were extracted. The response, prognoses and adverse events of these two regimens were evaluated.

Results: A total of 86 patients were included (cohort A: 49, cohort B: 36). Patients with histories of platinum-based chemotherapy were more allocated in cohort A. Though the response rates were similar in each cohort (44.9% in cohort A and 51.4% in cohort B, p = 0.83), the progression-free survival (PFS) was significantly more favorable in cohort A, as shown by the log-rank test (6.0 months vs 5.0 months; p = 0.027). The overall survival (OS) was also longer in cohort A, but there was no statistically significance (16.8 months vs 11.8 months; p = 0.072). In the Cox-regression hazard analysis, male sex (hazard ratio [HR] = 2.1, p = 0.010), older age (HR = 2.3, p = 0.018), PS 0 (HR = 2.2, p = 0.027), the absence of histories of platinum chemotherapy (HR = 3.2, p = 0.003) and the presence of tracheostoma (HR = 2.3, p = 0.018) were favorable factors of cohort A.

Conclusions: In our retrospective analyses, R/M SCCHN patients receiving weekly paclitaxel and cetuximab regimen (cohort A) and the EXTREME regimen (cohort B) were extracted. The response, prognoses and adverse events of these two regimens were evaluated.

Legal entity responsible for the study: Cancer Institute Hospital

Funding: Cancer Institute Hospital

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1004P Effect of Hedgehog signaling pathway on the proliferation of high-grade gliomas

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Background: High-grade gliomas are the most aggressive brain tumors. A clear understanding of the oncogenesis mechanisms and searching for specific targets among the proteins of signaling pathways involved in oncogenesis are needed to develop more effective therapy. According to current data, the Hedgehog pathway is involved in oncogenesis of glioma. In the case where the signal pathway is activated, GLI transcription factors alter the level of expression of the target genes, thus affecting the processes of proliferation, angiogenesis, chemoresistance, invasive and migratory activity. The aim of this study was to evaluate the effect of the activator (SHH) and inhibitor (cyclopamine) of Hedgehog signaling pathway on the proliferation of human glioma cell lines U87-MG, U251-MG and cells of human astrocytes.

Methods: Cell proliferation was investigated using xCELLigence system, which allows measurement of the electrical resistance of the gold microelectrodes located on the bottom of 16-well E-Plates. Results: It was shown that the SHH ligand increases proliferation of U251-MG cell line and human astrocytes. SHH ligand has no effect on proliferation of U87-MG cell line. Cyclopamine has an inhibitory effect on the proliferation of human glioma cell lines U87-MG and U251-MG, and has no effect on human astrocytes. Student’s-t test with significance level α = 0.05 was used for statistical analysis. Cyclopamine has an inhibitory effect on U251-MG culture, so we can assume that the pathway is active. Proliferation of U87-MG cell line was decreased. Spading of cyclopamine and adding SHH has no effect. The pathway also is active, but the addition of an activator does not provide additional stimulus. It can be assumed that the signaling pathway is most active. In human astrocytes cyclopamine has no effect on the proliferative activity of cells, and it is increased with the SHH addition. In this case the pathway is inactive, but SHH has an activating effect.

Conclusions: Our experiments with cyclopamine and SHH provide additional information for determining the activity of the pathway and help to develop a quantitative assessment of functioning Hedgehog signaling pathway in the known cell lines and in primary cell cultures.

Clinical trial identification: Extract from the protocol of the meeting of the Ethics Committee RNRMU named after Pirogov N.I. N131 dated January 27 2014

Legal entity responsible for the study: RNRMU named after Pirogov N.I.

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Disclosure: All authors have declared no conflicts of interest.

1005P Molecular analysis in serial biopsies in sinonasal mucosal melanoma

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Background: Melanomas from the mucosal surface are a rare entity, of which approximately 25% arise from the nasosinusial region. Given the low incidence of this entity, it is not well known the incidence of genetic alterations in sinonasal mucosal melanomas (SMM). The purpose of this study is to analyse mutational status of patients (pts) with SMM in primary tumors and in locoregional and/or distant relapse.

Methods: From 1988 to 2015, 25 pts were diagnosed of SMM in our institution. We collected formalin-fixed paraffin blocks from 19 primary tumors and, in 13 of them, from local recurrence and/or distant metastasis. Median number of samples per patient was 3 (range 1-9). We analysed the spectrum of mutations in KIT gene (exon 9, 11, 13 and 17) by standard PCR followed by Sanger sequencing, NRAS gene (exon 2, 3 and 4) by pyrosequencing and BRAF gene (exon 15) by Tagman PCR.

Results: The median age at diagnosis was 75 (range 42-86), 13 were males and 12 females. According to the TNM-SMM system, the pts were classified as T3 in 12 cases (48%), as T4 in 5 cases (20%), and 8 pts (32%) as T4b. 23/25 pts underwent surgery followed by radiotherapy, if needed, as first treatment and 2 pts received palliative chemotherapy with a DTIC-based schedule. 9/25 pts (36%) presented locoregional recurrence (36%) and 8/25 pts (32%) develop distant metastasis. We performed molecular analysis in 19 cases and we identified gene mutations in 5 cases, all from the nasal cavity. We found 2 cases (10.5%) with mutations in NRAS gene (both in exon 2: G12V) and 3 cases (15.8%) with mutations in KIT (all in the exon 11: RS686K, G656R, M53I). No BRAF mutations were detected. Interestingly, we found discrepancies in the NRAS mutational status of tumor samples obtained from 2 pts. In the first case, at diagnosis, we identified the NRAS mutation in 1 of 2 samples, and in 2 of 3 samples at the time of local recurrence. In the second case, the NRAS mutation was present at diagnosis but only in 2 of 4 samples of distant recurrence.

Conclusions: In our series of SMM, we have found a KIT mutation rate of 15.8% and a 10.5% in NRAS mutation. No BRAF mutations were detected. We have observed discrepancies in mutational status between different tumor samples in 2 pts with NRAS mutations that might be explained by tumor heterogeneity.

Legal entity responsible for the study: Hospital de la Santa Creu i Sant Pau and Laboratory on Oncology/Pangaea Biotech

Funding: Hospital de la Santa Creu i Sant Pau and Laboratory on Oncology/Pangaea Biotech

Disclosure: All authors have declared no conflicts of interest.
Expression profile of papillary thyroid carcinomas according to cervical lymph node metastasis status

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Background: A high incidence of lymph node metastasis has been described in papillary thyroid carcinoma (PTC), which is related to an increased risk of tumor recurrence. Biomarkers have potential to be used as predictive tool to identify patients with high risk to recur in comparison with imaging tests, which present low sensitivity to detect lymph node metastasis. The aim of this study is to identify molecular markers able to predict lymph node metastasis in PTC patients.

Methods: Messenger RNA sequencing data obtained from TCGA (Illumina HiSeq level 3) of PTC were used in a preliminary screening. From 897 patients, 280 were filtered to avoid confounding factors. Cases presenting lymph nodes (LN) positive (N1 = 107) had pathological confirmation of LN metastasis at diagnosis with unincinc primary tumor. Cases LN negative (N0 = 193) had pathological confirmation of LN disease free; they were not submitted to ablation by radiotherapy neither presented loco-regional recurrence after 1-year of follow-up. Differentially expressed genes were submitted to silico pathway analysis using the Reactome tool. Selected transcripts were further assessed by RT-qPCR using Tagman assays (Applied Biosystems) to confirm the findings in an independent set of 72 PTC samples.

Results: Based on TCGA database, 334 transcripts were detected by comparing N1 versus N0 patients (random variance t test FDR < 0.001 and fold change > 2). Pathway analysis revealed an enrichment of genes related to collagen degradation and formation, degradation of the extracellular matrix and activation of matrix metalloproteinases (FDR < 1%). From the 28 genes selected for validation by RT-qPCR, ARB1, S100A2, S100A10, SCEL and PDLIM4 were confirmed as higher expressed and DIO2 as lower expressed in N1 cases.

Conclusions: This study revealed a potential involvement of extracellular matrix remodeling pathways in the LN metastasis in PTC. In addition, ARB1, S100A2, S100A10, SCEL, PDLIM4 and DIO2 genes are promising markers to discriminate PTC tumors with higher risk of presenting cervical LN metastasis at diagnosis.

致癌率的预测
mandibular glands. These may be due to small sample size or short follow up period. Result of scan showed that PRP + PC are more effective than RPR

Legal entity responsible for the study: N/A

Funding: Mashad University of Medical Sciences

Disclosure: All authors have declared no conflicts of interest.

The role of interim FDG-PET after induction chemotherapy as a prediction of the efficacy of concurrent chemoradiotherapy in locally advanced squamous carcinoma of the head and neck

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Background: Having advantage for organ preservation and systemic control, induction chemotherapy (ICT) using doxetaxel, cisplatin and 5-FU (DCF) followed concurrent chemoradiotherapy (CCRT) has been used for nonsurgical management of locally advanced head and neck squamous cell carcinoma (HNSCC). Early prediction of efficacy of CCRT could be helpful to select patients with more effective in surgery than CCRT. We evaluated the role of interim 18-fluoro-2-deoxy-glucose positron emission tomography (FDG-PET) after ICT as a prediction of the efficacy of CCRT and clinical outcomes.

Methods: Tumor responses were retrospectively reviewed based on Response Evaluation Criteria in Solid Tumors after ICT and CCRT in locally advanced HNSCC. FDG-PET/ICT scans were performed in all patients before and after three cycles of DCF. We examined the association of metabolic response by the percentage decrease of maximum standardized uptake value (SUVmax) after ICT with complete response (CR) to CCRT and clinical outcomes including progression-free survival (PFS) and overall survival (OS).

Results: Forty-four patients with locally advanced HNSCC were evaluated with a median follow-up of 31.7 months. The SUVmax after ICT from baseline was more decreased in CR to CCRT group than non-CR group (78.8% vs. 62.5%, p = 0.004). A 78% decrease of SUVmax after ICT from baseline predicted CR after ICT (59.3% vs. 17.6%, p = 0.012), PFS (median, not reached vs. 15.0 months, p = 0.002) and OS (median, not reached vs. 43.3 months, p = 0.005) of the patients.

Conclusions: The SUVmax on interim FDG-PET after ICT could be useful to select patients benefiting from CCRT in locally advanced HNSCC and to predict survival outcomes.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

High expression of FOXM1 is a potential prognostic marker for oral squamous cell carcinoma patients treated with docetaxel-containing regimens

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Background: Forkhead box protein M1 (FOXM1) is an oncogene that regulates cell growth and differentiation, angiogenesis, apoptosis and aging and it is reported to play an important role in progression and drug sensitivity of various cancers. The purpose of this study was to determine whether FOXM1 expression could be a useful prognostic factor for oral squamous cell carcinoma (OSCC).

Methods: FOXM1 expression was investigated by immunohistochemistry in tissue samples of 56 OSCC patients treated with docetaxel (DOC)-containing regimens. In this study, we investigated the relationship between FOXM1 expression and clinicopathological features of OSCC, as well as the prognosis of above patients. Moreover, we examined the expression of FOXM1 in DOC-resistant human tongue carcinoma cell lines (HSC2/DOC, HSC3/DOC and HSC4/DOC) in vitro. We established these DOC-resistant cell lines by exposing HSC2, HSC3 and HSC4 parental cells to increasing concentrations of DOC over approximately two years.

Results: FOXM1 was detected both in nucleus and cytoplasm of OSCC tumor cells. FOXM1 expression in tumor tissues was significantly correlated with N classification (P = 0.0395), stage (P = 0.010), therapeutic efficacy (P = 0.0113) and outcome of patient (P = 0.0134); although there was no correlation between FOXM1 expression and patient’s gender, age or T classification. Moreover, high expression of FOXM1 in tumor cells was associated with shorter overall survival (OS, P = 0.0257). Multivariate analysis also revealed that high expression of FOXM1 was a predictor of reduced survival (P = 0.0327). Additionally, DOC-resistant OSCC cell lines showed significantly higher FOXM1 expression compared to the parental cell lines in vitro.

Conclusions: These findings suggest that high expression of FOXM1 in OSCC tumors is correlated with DOC resistance, as well as poor therapeutic effects and worse clinical outcomes in OSCC patients treated with DOC-containing regimen. Therefore, FOXM1 might have prognostic significance in oral squamous cell carcinoma patients.

Legal entity responsible for the study: Yamaguchi University Graduate School of medicine

Funding: Grant-in-Aid from the Japanese Ministry of Education, Science and Culture

Disclosure: All authors have declared no conflicts of interest.

A multi-institutional dose-finding and efficacy confirmation trial of superselective intra-arterial infusion of cisplatin and concurrent radiotherapy for patients with locally advanced maxillary sinus cancer (JCOG1112, RADPLAT-MSC): Results of dose-finding phase

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Background: Superselective intra-arterial infusion of high-dose cisplatin with concurrent radiotherapy (RADPLAT) has been performed for the patients with locally advanced maxillary sinus squamous cell carcinomas (LA-MSSCC) in several institutions and has been reported to result in a favorable survival. This multi-institutional prospective trial was aimed to confirm the adequate dose and efficacy of RADPLAT for the patients with LA-MSSCC. The dose-finding phase was performed to evaluate the incidence of dose-limiting toxicity (DLT) and to determine the recommended cycle of intra-arterial infusion of cisplatin.

Methods: Eighteen patients were registered from 7 institutions for this study. In this dose-finding study, 100 mg/m² of cisplatin was administered intra-arterially weekly for 7 weeks with concomitant radiotherapy (total 70 Gy). Cisplatin was skipped in the case of adverse events that met the stopping rule defined by the protocol. The recommended number of cycles was determined according to the distribution of the number of cycles of administered cisplatin and the incidence of DLT.

Results: The median age of all participants was 64 years old (range, 40-75 years old). Sixteen patients were diagnosed as T4aN0M0, and two patients as T4aN0M1. All patients achieved full dose of radiotherapy. The number of cycles of administered cisplatin was 7 in 13 patients and 6 in 5. DLT was observed in 5 patients; Gr 3 liver dysfunction (1), Gr 4 thrombocytopenia (1), Ccr < 40 (1), Gr 3 retinopathy (1), and Gr 3 retinal detachment (1). There was not either treatment-related death or neural complication.

Conclusions: RADPLAT appears to be safe and well-tolerated at 7 cycles of cisplatin at a dose of 100 mg/m² each cycle, which were determined to be the recommended number of cycles for LA-MSSCC.

Clinical trial identification: UMIN000013706.

Legal entity responsible for the study: N/A

Funding: Research Funding Source Name: the Practical Research for Innovative Cancer Control(15ck0106137h0002)

Disclosure: All authors have declared no conflicts of interest.

Cervical lymph node metastasis of squamous cell carcinoma of an unknown primary (SCCUP): a single institutional review

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Background: Squamous cell carcinoma of unknown primary (SCCUP) represents 1% of all head and neck malignancies. Five-year survival rates of 30% to 50% are reported with radical neck surgery, high-dose radiotherapy (RT) and combination modalities.

Methods: A retrospective analysis from chart review of all consecutive non metastatic SCCUP patients (pts) diagnosed and treated at our Institution between January 2009 and December 2014 was performed. Primary aim was to evaluate the clinical, demographic and treatment data. Secondary aim: to evaluate overall survival (OS) and
Results: From a total of 80 pts, 66 (82%) were males and 14 (18%) were females with a median age of 62 years (range 41-84). Alcohol and tobacco abuse was found in 69 and 76% of pts, respectively. Diagnostic evaluation consisting of PET-CT, cervical and thoracic CT-scan, ENT examination and laryngoscopy, endoscopy and bronchoscopy were completed in 33 (41%) of pts. Distribution of pts by N status was N1 -5 pts, N2a -2 pts, N2b- 31 pts, N2c– 3pts and N3 - 34 pts. Level node IV/v involvement was seen in 56 pts. Extracapsular spread was found in 54 (67%) pts and G3 in 32 (40%) pts. Upfront neck dissection (ND) with biopsy of base of tongue and hypopharynx and bilateral amigdallectomy were performed in 51 pts (64%), and in 42 of these pts was followed by adjuvant treatment (RT in 17, chemo/ radiation (CRT) in 25). Two pts received definitive CRT, 10 isolated RT and 9 induction chemotherapy followed by CRT. Eight pts were treated with best supportive care. Seven cervical and 16 systemic (lung in 1 pt) recurrences were documented. In the multivariate analysis, ND significantly affected survival (non-surgery group hazard ratio 5.7 95CI95% 2.93-11.2), p < 0.0001. The 3- and 5-years OS rate and EFS rate was 55%/53% and 37%/ 35%, respectively.

Conclusions: Despite the N-stage being higher than expected, our survival data were similar to the published literature. The only prognostic factor for survival in our pts was upfront neck dissection. Other prognostic factors were not statistically significant probably due to the small sample.

Legal entity responsible for the study: Instituto Português de Oncologia de Lisboa Francisco Gentil EPE

Funding: Instituto Português de Oncologia de Lisboa Francisco Gentil EPE

Disclosure: All authors have declared no conflicts of interest.

Table 1014P: Patients and tumor characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man/Female</td>
<td>80/20</td>
</tr>
<tr>
<td>Age (median)</td>
<td>57</td>
</tr>
<tr>
<td>First primary tumor characteristics</td>
<td></td>
</tr>
<tr>
<td>Stage (I/II/IV Unknown)</td>
<td></td>
</tr>
<tr>
<td>Surgery Radiotherapy (RT)</td>
<td>26.8 6 8.6 37.5 57</td>
</tr>
<tr>
<td>Chemotherapy (CT) i RT surgery</td>
<td>34.3 29 20 5 31 4 57</td>
</tr>
<tr>
<td>Surgery + QT + RT surgery</td>
<td>57</td>
</tr>
<tr>
<td>Second primary tumor</td>
<td></td>
</tr>
<tr>
<td>Oral cavity Oropharynx Larynx Esophagus Others</td>
<td>28.7 25 26 1 143</td>
</tr>
<tr>
<td>Local /loco-regional affection Metastatic Unknown</td>
<td>37 14 5 7 15 5 57</td>
</tr>
<tr>
<td>Surgery Radiotherapy (RT) Chemotherapy (CT) i RT surgery</td>
<td>11.5</td>
</tr>
<tr>
<td>Surgery + QT + RT surgery</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>28.4 8 6 2.9</td>
</tr>
</tbody>
</table>

Conclusions: SPT represents the leading long-term cause of mortality in these patients. SN or MN of SPT was the only independent predictor of lower OS in our study. If we identified features that predile the highest risk for the appearance of SPT, follow-up could be optimized for patients with higher risk.

Legal entity responsible for the study: Hospital Universitario La Fe
is a randomized, open-label, phase 3 study comparing the combination of nivo and ipi with the Extreme regimen as 1L therapy in pts with R/M SCCHN.

**Trial design:** Pts aged ≥18 yr with histologically confirmed R/M SCCHN with non-amenable to curative therapy who have received no prior systemic therapy for their disease (except chemotherapy given as part of a multilmodal treatment regimen that was completed >6 mo or before enrollment) will be eligible. Approximately 490 pts will be randomized to receive nivo in combination with ipi or the Extreme regimen until progression or unacceptable toxicity. Primary endpoints are OS and progression-free survival. Secondary endpoints are objective response rate, time to symptomatic deterioration based on the 10-item Functional Assessment of Cancer Therapy-Head & Neck Symptom Index, and PD-L1 expression as a predictive biomarker for efficacy.

**Clinical trial identification:** NCT02741570

**Legal entity responsible for the study:** Sponsored by Bristol-Myers Squibb.

**Funding:** Sponsored by Bristol-Myers Squibb.

**Disclosure:** A. Argiris: Consultant for BMS. M. Gillison: Consultant and clinical trials contract to OSU with Bristol-Myers Squibb. Consultant for Merck & Lilly. R.L. Ferris: Grant received from Ventrx, Bristol-Myers Squibb, and AZ/Medimmune. Member of ad-hoc advisory board for Merck, Celgene, Bristol-Myers Squibb, AZ/Medimmune, and BMS. K. Harrington: Advisory Board member for BMS. A. Argiris: Consultant for BMS.

**Background:** Local/Regionally recurrent squamous cancers of the head and neck following radiotherapy are often not amenable to surgical salvage. Conventionally fractionated re-irradiation has been investigated, but survivals are poor. Stereotactic radiotherapy (SBRT) has been proposed as an alternative to conventionally fractionated re-irradiation, but reports to date have not shown significantly improved outcomes. Cisplatin has been shown to sensitize squamous carcinomas to radiotherapy even at doses > 7 Gy. We therefore designed a phase I dose escalation study of SBRT for re-irradiation with concurrent cisplatin (MCC 17799, ClinicalTrials.gov: NCT02158324).

**Trial design:** This is a phase I, open label, dose escalation safety and tolerability study of SBRT in combination with cisplatin in patients with locally or regionally recurrent squamous cell carcinoma of the head and neck with prior radiotherapy > 45 Gy. Cohort 1 will receive 30 Gy SBRT given every other day for 5 fractions with cisplatin at 15 mg/m² prior to each fractionation. Dose escalation will be performed using an empiric design based on evaluation of dose limiting toxicities up to 60 days following therapy. Approximately 15 patients will be enrolled at our institution. The primary endpoint is to define the maximum tolerated dose of concurrent cisplatin and SBRT. Secondary endpoints include loco-regional control, overall survival, and adverse events.

**Clinical trial identification:** MCC 17799, ClinicalTrials.gov: NCT02158324

**Legal entity responsible for the study:** N/A

**Funding:** Department of Radiation Oncology, Moffitt Cancer Center

**Disclosure:** All authors have declared no conflicts of interest.

**Phase 1b trial of LY2060368 in combination with chemoradiation in patients with locally advanced head and neck squamous cell cancer

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**Background:** Checkpoint Kinase 1 (CHK1) is a multifunctional protein kinase and regulator of DNA damage response. LY2060368, an ATP-competitive inhibitor of CHK1, has been tested in Phase 1 studies as a monotherapy and in combination with cytotoxic and targeted agents. Objective responses have been observed following exposure to LY2060368 monotherapy in patients with squamous cell tumors, including head and neck cancer (HNSCC). Transient Grade 4 neutropenia (typically <5 days) is the primary toxicity.

**Trial design:** This study is a two-part multicenter, parallel, non-randomized, open-label Phase 1b trial (NCT02555644) in patients with newly diagnosed locally advanced untreated HNSCC. The primary objective is to determine the recommended Phase 2 dose (RP2D) of LY2060368 in combination with either cisplatin and radiation therapy (RT) (Part A) or cetuximab and RT (Part B). Secondary objectives include an evaluation of pharmacokinetics, safety/toxicity, and preliminary efficacy. Key inclusion criteria include: patients ≥18 yr with newly diagnosed stage III, IVa, or IVb HNSCC of oropharynx, hypopharynx, or larynx. Key exclusion criteria include: received prior systemic therapy for the study cancer, radiation therapy to head and neck region, or curative intent surgery in head and neck region; evidence of distant metastatic disease; serious heart condition, such as congestive heart failure, unstable angina pectoris, or heart attack within the last three months; and family history of long corrected QT interval (QTC) syndrome. Part A patients will receive 40 mg/m² cetuximab weekly for 7 weeks, while patients in Part B will receive cetuximab weekly at an initial dose of 400 mg/m² followed by 250 mg/m² for 7 weeks. All patients will receive ~70 Gy RT delivered at 5 fractions/week over 7 weeks and LY2060368 as a 1 hour infusion every 2 weeks. Dose escalation of LY2060368 will be performed using modified time-to-event Continual Reassessment Method (TITE-CRM). Following escalation and the determination of the RP2D for each arm, expansion cohorts of approximately 15 patients will be enrolled to confirm the dose.

**Clinical trial identification:** NCT02555644

**Legal entity responsible for the study:** Eli Lilly and Company

**Funding:** Eli Lilly and Company

**Disclosure:** E. Yang: Research support from Eli Lilly and serve on advisory board for Nanion Technologies. W. Zhang, A. Fink, A.B. Lirip: Employee of Eli Lilly and Company and a minor stockholder. A.B. Lirip: I and my husband are employees of Eli Lilly and Company and a minor stockholder. E. Deutsch: Grant for preclinical research through Gustave Roussy cancer campus. All other authors have declared no conflicts of interest.
heterogeneous designs often provide the first evidence of efficacy at the group or class level and are followed by additional studies to better understand the underlying effect. CII data can be used to track the impact of the current transition toward smaller, targeted studies. Our results highlight the need for timely and data-driven tracking of progress across the spectrum of cancer research and fast learning from real-world evidence to validate outcomes.

Conclusions: We make the CII freely available to all stakeholders and encourage users to perform their own custom analyses. https://pacenetworkusa.com/

Legal entity responsible for the study: Eli Lilly and Company; Rose Li and Associates, Inc.

Funding: Eli Lilly and Company


Are the newer chemotherapy drugs worth their high cost? - A survey of UK public’s perception of reasonable price for chemotherapy drugs according to their health benefit

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Background: The cost of oncology drugs has skyrocketed recently. Many newly approved drugs have modest survival benefits only a few extra months. In USA, newer oncology drugs place a direct heavy economic burden on patients who make huge co-payments out of pocket (Saltz JCO 2015;33:1093-4). In UK the burden falls on the taxpayer. A face to face survey was done to assess UK public’s perception of reasonable price for a course of chemotherapy drug relative to their potential benefits.

Methods: A ‘tick box’ survey form with 15 price bands (low to high) including a free text box was used. (Price Bands: £0 to £5K, 5 to £10K, 10 to £20K, 20 to 30K, 30 to 40K, 40 to 50K, 50 to £100K, 100 to £250K, 250 to £500K, > £500K). Place of recruitment: (1) Market Town of Chesterfield: 20 recruited, 15 declined (2) City of Nottingham 61 recruited, 23 declined. Recruitment period: March 2015. Survey done by Clinical research nurse or medical student on oncology elective. The regional ethics committee advised that a formal ethical approval is not needed for public surveys in public places.

Results: Female 53%, Mean age 36 yrs (range 16 to 87 yrs). Subjects suggested a significantly lower value as a reasonable price for a course of cancer drugs even when drugs have significant curative potential. (Table). Only a small minority felt that drug costs of more than 100,000 British pounds are reasonable. Because UK has a taxpayer funded health service, UK public probably have very poor knowledge about the actual cost of chemotherapy drugs.

Conclusions: The survey results indicate that the UK public might be willing to politically support value based commissioning if it is done in a fair and explicit manner.

Table: 1023P

<table>
<thead>
<tr>
<th>What price do you think it is reasonable for a pharmaceutical company to charge for the chemotherapy drug ……..</th>
<th>Less than 10,000 British pounds</th>
<th>10,000 to 100,000 British pounds</th>
<th>More than 100,000 British pounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>If drug cures 1 in 2 cancer patients (50% cure rate)</td>
<td>58%</td>
<td>27%</td>
<td>15%</td>
</tr>
<tr>
<td>If drug cures 1 in 5 cancer patients (20% cure rate)</td>
<td>67%</td>
<td>22%</td>
<td>11%</td>
</tr>
<tr>
<td>If drug does not cure but makes cancer patients live longer by an extra 6 months</td>
<td>69%</td>
<td>26%</td>
<td>5%</td>
</tr>
<tr>
<td>If drug does not cure but makes cancer patients live longer by an extra 3 months</td>
<td>83%</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>If drug does not cure and does not make a cancer patient live longer but relieves cancer related pain and other symptoms</td>
<td>89%</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>

chi square test for all q p < 0.001. N: 100,000 British pounds was equivalent 137,000 Euros and 148,000 US dollars at time of survey.

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Legal entity responsible for the study: N/A
Funding: N/A
Disclosure: All authors have declared no conflicts of interest.

1024P
Methodological differences and the appropriate application of oncology value frameworks to assess clinical value
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Background: A number of value frameworks have been developed recently as tools to evaluate new oncology products. The frameworks differ in stated objectives and methodology, and each uses a different set of criteria for evaluating products. We compare and contrast the frameworks, to identify the important differences and similarities between them, and conclude with the implications for clinical decision-making.

Methods: The methodologies of six value frameworks (ASCO, NCCN, ESMO, MSKCC, DrugAbacus, and ICER) were reviewed. Using the published scoring systems where available, we evaluated 33 recently approved oncology drugs by scoring them against individual framework criteria, using published data from pivotal trials. We compared results and identified the origins of the differences in scoring outcomes within the underlying methodologies.

Results: The range of approaches to assessing clinical value, both in terms of assigning scores and the relative importance given to those scores, can produce considerable variability in the value assigned to a treatment in different value frameworks. Scoring frameworks are often complex and some important aspects remain subjective. Specific attributes, such as whether a treatment is considered to have curative potential or the pivotal trial is a single-arm Phase 2 study, have a significant bearing on value framework scores and the reasons for assigning this level of impact are not clear.

Conclusions: Understanding the methodology employed by a value framework to assess clinical value is critical to interpreting the scores of a product within it. The assessed clinical value of a treatment can depend on assumptions made during the assessment of efficacy and safety and the context in which the assessment takes place. To avoid inconsistencies in clinical decision-making and unintended consequences on incentives for innovation, the results of value frameworks should be used cautiously. Further evolution of value frameworks will be necessary to produce more transparent and robust tools for decision-makers.

Legal entity responsible for the study: PRMA Consulting Ltd
Funding: PRMA Consulting Ltd

1025P
The cost-effectiveness of combination therapy: Challenges of the present, solutions for the future? A myeloma analysis
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Background: The number of treatments for cancer has increased over recent years. Monotherapy for some malignancies delivers only marginal benefit, whilst combination therapy (CT) improves results by using synergistic mechanisms of action. CT increases treatment cost however, and in an era of healthcare constrained by cost-containment, national reimbursement of CT conditional on cost-effectiveness is challenging. This research assesses drivers of CT cost-effectiveness, using myeloma as an example, to inform approaches to evidence based approaches to reimbursement.

Methods: A 3-state cost-effectiveness model (pre-progression; post-progression; dead) for front-line treatment of myeloma was developed. Continuous lenalidomide + dexamethasone (Ld) data were extracted from published results and, using parametric modelling, extrapolated to 20 years, with costs based on UK prices. Add-on drug X was assumed to deliver survival benefit (PFS HR = 0.7; OS HR = 0.7), be dosed QW (if priced less than £2,000) and halved dosing cost (£4,000/month). Scenario analyses considering differing evidence and treatment approaches included: improved PFS and OS reduced dosing schedules; limited treatment duration; use as a doublet (i.e. Xd); reduced Drug X cost.

Results: Combination therapy Ld compared with Xd resulted in a base-case incremental cost-effectiveness ratio (ICER) of £111K/QALY. Scenario analysis representing 28.5% improvement in both PFS (ICER = £139K/QALY) and OS (ICER = £498K/QALY) did not substantially improve CE. In contrast, scenarios which induced substantial cost savings improved CE (X dosed QW, ICER = £69K/QALY; X cost £1,000/dose, ICER = £464K/QALY; halved Ld dosing, ICER = £88K/QALY; 24-month treatment cap, ICER = £898K/QALY, doubled, ICER = £996K/QALY).

Conclusions: Clinical trials assess clinical outcomes, however these results suggest clinical outcomes alone may be insufficient to establish CT cost-effectiveness in myeloma. Pursuit of economic benefit beyond clinical outcomes, including resource-sparing approaches to treatment, may mitigate this risk and facilitate national reimbursement, and should therefore be considered in clinical trial design.

Legal entity responsible for the study: Bristol-Myers Squibb
Funding: Bristol-Myers Squibb

1026P
A shared-risk model linking patient-level clinical outcomes and drug company reimbursement in cancer care
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Background: Pharmaceutical companies are investing heavily in the development of compounds with similar mechanism of action to that of drugs already on the market. New and potentially expensive medications are then approved with minimal if any advantage over existing drugs. We suggest a value-driven model that will tie the economic gains of drug companies offering new anti-cancer drugs to the clinical outcomes.

Methods: We focused on advanced colorectal cancer that progressed after 1st-line chemotherapy. PFS Kaplan-Meier curves of five common drugs were analyzed (1-5). “Integrated” PFS (iPFS) was defined as the mean of median PFSs of those drugs. For the subset of patients (in those studies) whose disease progressed earlier than a defined iPFS cutoff, the manufacturer were to lose a certain fraction of revenues. For the subset of patients with sustained response longer than a defined iPFS cutoff, the manufacturer were to gain extra profits. Total extra revenues and losses for all companies were to equal zero. Drugs prices and incidence rates were derived from DrugAbacus and American Cancer Society websites. A mathematical calculation was done to show model feasibility.

Results: iPFS thresholds chosen were 1 and 0.7. For every patient with no progression at 1 iPFS, the company were to gain a randomly-selected value of 30% of launch price. To maintain net zero financial loss/gain for all manufacturers together, it was calculated that companies should lose 41.4% of launch price for every patient who progressed before 0.7 iPFS. With model application, Amgen, Regeneron and Eli Lilly achieved revenues of 105.6% to 109.7% compared with non-model settings. These profits amounted to extra annual gains of approximately 25 million dollars (Amgen) and 53 million dollars (Regeneron). Bristol-Myers and Genentech lost 18.7% and 3.1% of anticipated revenues, respectively. Their absolute annual deductions approximated 8 million dollars (Genentech) and 105 million dollars (Bristol-Myers).

Conclusions: A shared-risk model of cancer drug reimbursement would create a potent incentive for companies to develop medications that significantly improve the overall value of existing compounds.

Legal entity responsible for the study: Qad Oren
Funding: N/A
Disclosure: All authors have declared no conflicts of interest.

1027P
Novel therapy options for advanced & metastatic melanoma patients in EU5 countries result in a changing treatment pattern especially in BRAF mutant patients
M. Bernhard, T. Schmitt, K. Acker
IMS Global Oncology, IMS Health GmbH & Co. OHG, Frankfurt, Germany

Background: Real world data on treatment (TX) patterns in advanced and metastatic melanoma is of great value to demonstrate the use of novel therapy options. We provide an overview about the application of diagnostic marker testing and its implication on melanoma TX patterns in regard to novel targeting drugs that recently entered the market.

Methods: This study is based on IMS Oncology Analyzer™, a quarterly physician panel survey including anonymous retrospective patient (PT) data about disease and TX history, across all cancer types. Melanoma PTs treated within the year 2013 and 2015 in EU5 countries (France, Germany, Italy, Spain and UK) were analyzed.

Results: In 2013, 45.7% of adv. & met. melanoma PTs received chemotherapy (CT). In contrast, 85% of PTs received a targeted therapy including anti-PD1/PD-L1 TXs. Distribution of the PTs according their BRAF status shows that 2% of BRAF mutant (MUT) but ∼10% when BRAF WT PTs are treated with CTs in their first line in 2015.

Abstracts | Annals of Oncology

Volume 27 | Supplement 6 | October 2016
Table: 1027P

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>2013</th>
<th>2015</th>
</tr>
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<tr>
<td>IIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Pts included in a clinical trial or not receiving a systemic therapy were not considered. Pts with an unknown BRAF status or Pts awaiting test results were excluded. Table 1: Stage III/IV melanoma 1st line T\x=req.5 cm landscape

Conclusions: This study indicates a switch towards targeted therapies accounting for more than 80% of 1st line melanoma therapies in 2015. Hereby, the information on the BRAF status is crucial and determines the TX decision in regard of the drug type. However, nearly 20% of BRAF WT Pts receive CTs in their 1st line irrespective of novel available therapy options. Further research is necessary to understand the missing uptake of novel TX options and the related clinical practice.

Legal entity responsible for the study: IMS Health GmbH & Co. Ohg

Funding: IMS Health GmbH & Co. Ohg

Disclosure: M. Bernhardt, N. Schmidt, K. Acker: Employee of IMS Health

1028P

The relative clinical value of immun-oncology treatment, the NNT values of PD-1-inhibitor nivolumab and pembrolizumab in metastatic melanoma patients

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1Chemical Oncology, National Institute of Oncology, Budapest, Hungary, 2Health Insurance, University of Pecs, Pecs, Hungary

Background: The immun-oncology innovations of cancer treatment, the PD-1 inhibitor pembrolizumab and nivolumab were registered by EMA for the treatment of metastatic melanoma. The monoclonal, humanized, IgG4k antibody pembrolizumab and the human inhibitor nivolumab block the PD-L1 and/or PD-L2 interactions and enhance the antitumor immune response of T cells. The current outcome measures do not assess the long-term benefit of I-O therapies. In the Keynote-002 ipi refractor group, the pembrolizumab 2mg/kg arm CR was 2%, PR 19%, and SD 18%. In the 10 mg/kg pembrolizumab arm CR was 3%, PR 23%, SD 18%. In the chemotherapy group, IC, there was no CR, while PR occurred in 4%, SD in 18%.

Methods: To evaluate the efficacy of pembrolizumab and nivolumab, to measure their relative clinical value by calculating NNT, the number of patients who need to be treated to prevent one death. We analyze the survival data and calculated the NNT values of the Phil Keynote-002 study pembrolizumab vs IC in ipi refractor group, the PhilII Keynote-006 study pembrolizumab vs ipi group, the PhilII CheckMate-066 study nivolumab vs DTC group data.

Results: In the Keynote-002, the 2mg/kg pembrolizumab arm NNT=3.8, the NNT value of the 10mg/kg group: 4.5. In the Keynote-006 pembrolizumab vs ipi study, the 1Y OS rate was 73.4% in the 10mgQ2W group, 68.4% in the 10mgQ3W group, and 58.2% in the ipi group. The NNT of the 10mgQ2W patient group: 4.67, the NNT of the 10mgQ3W was 6.66. In the CheckMate-006 study the nivolumab group Y1OS 70.7%, the estimated Y2 OS was 57.7% and the DTC group Y1OS was 46.3% and Y2 26.7%. The NNT value of nivolumab group was 4.16-9.17.

Conclusions: Based on Phil-III studies, the NNT values of novel immunotherapies demonstrate the exceptional relative clinical value of PD-1 inhibitors. The prevention of one death, their clinical value is based on their NNT values, pembrolizumab: 3.8-6.6, nivolumab 4.16-9.17. These results show the future potential of I-O clinical benefit. Over the follow up time the risk reduction is not constant it is recommended to calculate the NNT values at least twice, not only at one specific time point, if necessary data are available from the trials.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

1029P

Real-world comparative effectiveness analysis of second-line (2L) nab-paclitaxel (nab-P) vs eribulin (Erib) in patients (Pts) with metastatic breast cancer (MBC)

C. Pelletier1, M. Parisi, S. Glück, Q. Ni, F. Braiteh

1U.S. Health Economics and Outcomes Research, Celgene Corporation, Summit, NJ, USA, 2Pancreatic Cancer and Immuno-Oncology, Celgene Corporation, Summit, NJ, USA, 3Oncology, University of Nevada School of Medicine and Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA

Background: nab-P monotherapy is approved for 2L treatment (Tx) of MBC. This real-world analysis evaluated comparative effectiveness of 2L nab-P vs Pac in pts with MBC.

Methods: A retrospective cohort study was performed using fully de-identified data from a US electronic medical record platform of 1300 community (not university-based) oncologists. This analysis included pts with MBC who initiated 2L nab-P or Pac monotherapy from 12/1/10 to 4/6/15 (± 2 doses of nab-P or Pac required to be included in the analysis). The primary objectives were to time to discontinuation (TTD) and time to next Tx (TTNT). Adverse events (AEs) and supportive care were also examined. Subanalyses in pts with hormone receptor-positive (HR+)/human epidermal growth factor receptor-2-negative (HER2−) or triple-negative (TN) MBC were conducted.

Results: This analysis included 411 pts (109 treated with nab-P Tx and 302 with Pac Tx). Pts treated with nab-P were older (mean 61 vs 57) and more frequently had HR+ (78% vs 65%) or HER2− (83% vs 79%) disease. Most pts received weekly Tx (Table). Prior use of a taxane or concurrent use of a targeted agent was similar between groups. nab-P was associated with significantly longer TTD vs Pac. TTNT was similar between groups. Pts treated with nab-P had less fatigue, pain, and neurophoria but more nausea and vomiting vs Pac. Antiemetics (IV) and Tx for hydration and allergic reaction were used less with nab-P, and Tx for bone loss and granulocyte colony-stimulating factor (G-CSF) were used less with Pac. Tx in favor of nab-P was shown in pts with HR+/HER2− or TN MBC, and TTNT was numerically longer with nab-P vs Pac in pts with HR+/HER2− or TN MBC.

Table: 1029P

<table>
<thead>
<tr>
<th>Overall population</th>
<th>nab-P n = 109</th>
<th>Pac n = 302</th>
<th>Unadjusted P-value</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx schedule, weekly, n (%)</td>
<td>89 (83)</td>
<td>286 (95)</td>
<td>0.016</td>
<td>0.001</td>
</tr>
<tr>
<td>TTID, median, mos</td>
<td>4.5</td>
<td>2.8</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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<tr>
<td>TTNT, median, mos</td>
<td>5.9</td>
<td>4.2</td>
<td>0.014</td>
<td>0.214</td>
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<tr>
<td>Any grade AE in 5% pts, %</td>
<td>45.0</td>
<td>58.3</td>
<td>0.017</td>
<td>0.032</td>
</tr>
<tr>
<td>Overall</td>
<td>66.5</td>
<td>65.9</td>
<td>0.505</td>
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<tr>
<td>Neutropenia</td>
<td>15.6</td>
<td>10.6</td>
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<td>0.243</td>
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<td>13.6</td>
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<td>Pain</td>
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<tr>
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<tr>
<td>Diarrhea</td>
<td>2.8</td>
<td>7.0</td>
<td>0.109</td>
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</table>
| NNT values of PD1-inhibitor nivolumab and pembrolizumab in metastatic melanoma patients

E. Porneczy1, I. Boncz2

1U.S. Health Economics and Outcomes Research, Celgene Corporation, Summit, NJ, USA, 2Pancreatic Cancer and Immuno-Oncology, Celgene Corporation, Pecs, Hungary

Background: Immun-oncology innovations of cancer treatment, the PD-1 inhibitor pembrolizumab and nivolumab were registered by EMA for the treatment of metastatic melanoma. The monoclonal, humanized, IgG4k antibody pembrolizumab and the human inhibitor nivolumab block the PD-L1 and/or PD-L2 interactions and enhance the antitumor immune response of T cells. The current outcome measures do not assess the long-term benefit of I-O therapies. In the Keynote-002 ipi refractor group, the pembrolizumab 2mg/kg arm CR was 2%, PR 19%, and SD 18%. In the 10 mg/kg pembrolizumab arm CR was 3%, PR 23%, SD 18%. In the chemotherapy group, IC, there was no CR, while PR occurred in 4%, SD in 18%.

Methods: To evaluate the efficacy of pembrolizumab and nivolumab, to measure their relative clinical value by calculating NNT, the number of patients who need to be treated to prevent one death. We analyze the survival data and calculated the NNT values of the Phil Keynote-002 study pembrolizumab vs IC in ipi refractor group, the PhilII Keynote-006 study pembrolizumab vs ipi group, the PhilII CheckMate-066 study nivolumab vs DTC group data.

Results: In the Keynote-002, the 2mg/kg pembrolizumab arm NNT=3.8, the NNT value of the 10mg/kg group: 4.5. In the Keynote-006 pembrolizumab vs ipi study, the 1Y OS rate was 73.4% in the 10mgQ2W group, 68.4% in the 10mgQ3W group, and 58.2% in the ipi group. The NNT of the 10mgQ2W patient group: 4.67, the NNT of the 10mgQ3W was 6.66. In the CheckMate-006 study the nivolumab group Y1OS 70.7%, the estimated Y2 OS was 57.7% and the DTC group Y1OS was 46.3% and Y2 26.7%. The NNT value of nivolumab group was 4.16-9.17.

Conclusions: Based on Phil-III studies, the NNT values of novel immunotherapies demonstrate the exceptional relative clinical value of PD-1 inhibitors. The prevention of one death, their clinical value is based on their NNT values, pembrolizumab: 3.8-6.6, nivolumab 4.16-9.17. These results show the future potential of I-O clinical benefit. Over the follow up time the risk reduction is not constant it is recommended to calculate the NNT values at least twice, not only at one specific time point, if necessary data are available from the trials.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
Table: 1033P

<table>
<thead>
<tr>
<th></th>
<th>nab-P (n = 107)</th>
<th>Eribulin (n = 69)</th>
<th>Unadjusted P Value</th>
<th>Adjusted P Value</th>
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<tr>
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<td>60</td>
<td>61</td>
<td>0.686</td>
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<td>Schedule, %</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>TTD, median, mos</td>
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<tr>
<td>Fatigue</td>
<td>2.8</td>
<td>7.2</td>
<td>0.266</td>
<td>-</td>
</tr>
<tr>
<td>Pain</td>
<td>2.8</td>
<td>7.2</td>
<td>0.266</td>
<td>-</td>
</tr>
<tr>
<td>Supportive Care costs/100 days</td>
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<td>6.92</td>
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<td>5.47</td>
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<td>Tx for hydration</td>
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<td>3.70</td>
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<tr>
<td>Tx for bone loss</td>
<td>1.90</td>
<td>2.05</td>
<td>0.452</td>
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<tr>
<td>G-CSF</td>
<td>1.44</td>
<td>3.16</td>
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<td>&lt;0.001</td>
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<tr>
<td>HR + HER2+</td>
<td>n Median, n Median,</td>
<td>9.0</td>
<td>4.5</td>
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<td>TTD</td>
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<td></td>
<td>67.4</td>
<td>62.7</td>
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<td></td>
<td>59.9</td>
<td>64.4</td>
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<td>20.3</td>
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<td></td>
<td>13.0</td>
<td>11.7</td>
<td>0.794</td>
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</table>

Conclusions: In this US-based, real-world analysis, TTD and TTNT were numerically longer with nab-P compared with Erib, including in the HR + /HER2− and TN subsets. AEIs were similar between the 2 groups. Pts receiving nab-P required less supportive care.

Legal entity responsible for the study: Monika Parini, MPH

Funding: Celgene Corporation

Disclosure: M. Parini, S. Glück, C. Pelletier, Q. Ni Mr: Employee of Celgene Corporation. F. Braiteh: AbbVie, ActiveBioTech, Amgen, AstraZeneca, Bayer, BMS, BIND, BioMarin, BioTheranostics, BI Therapeutics, BI, Caris, G2 Therapeutics, Celgene, Daichi, Dendreon, Genomic Health, Gilead, GSK, Halozyme, Heron, Eli Lilly, Incyte, Insys, Novartis, Pfizer, etc.

1033P Cost-effectiveness analysis (CEA) of adjuvant trastuzumab therapy use in HER2-positive early-stage breast cancer (EBC)

K. L. Quintyne1, B. Woulé2, A. Deei3, R. Gupta2

1Community Oncology, National Cancer Control Programme (NCCP), Dublin, Ireland; 2Mid-Western Regional Hospital, Limerick, Ireland; 3Public Health, HSE Mid-West, Limerick, Ireland

Background: Adjuvant treatment options for HER2-positive early-stage breast cancer (EBC) have expanded in recent years. Trastuzumab has been shown in several randomized controlled trials (RCTs) to offer significant survival advantage in patients with high-risk HER2-positive EBC. This study aimed to estimate cost-effectiveness of adjuvant trastuzumab therapy compared to standard chemotherapy alone in patients with HER2-positive EBC in Ireland.

Methods: A CEA was performed using a decision-tree model using estimate outcomes and costs over a 10-year period using a cohort of women with HER2-positive EBC, treated with or without 12 months of trastuzumab after adjuvant chemotherapy alone. These patients received ambulatory care in the Department of Medical Oncology (DoMO), University Hospital Limerick (UHL). Transition probabilities were derived from the perspective of the Irish healthcare system. Both costs and outcomes were discounted by 3%. One-way sensitivity analysis was undertaken to assess the associated uncertainties in the expected output measures.

Results: In this study group, our model showed that adjuvant trastuzumab treatment in HER2-positive EBC, yield 8.54 quality-adjusted life-years (QALY) compared to adjuvant chemotherapy alone. Adjuvant trastuzumab treatment yielded an incremental cost-effectiveness ratio (ICER) of €42,801.62 per QALY.

Conclusions: It has been shown that for a 10-year time horizon, adjuvant trastuzumab is a cost-effective therapy for patients with HER2-positive, high-risk EBC (i.e. less that €45,000/0.00 threshold set in Republic of Ireland).

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

1033P Cost-effectiveness of nivolumab in patients with advanced renal cell carcinoma in Sweden

S. Johal1, K.M. Johannesen2, B. Malcolm3, J. Doan4

1Health Economics, PARAXEL Access Consulting, London, UK; 2Worldwide Health Economics & Outcomes Research, Bristol-Myers Squibb, Princeton, NJ, USA

Background: In the CheckMate 025 study (NCT01668784), nivolumab improved overall survival (OS) versus everolimus in previously treated patients with advanced renal cell carcinoma (N Engl J Med 2015;373:1803–13). We evaluated the cost-effectiveness of nivolumab versus everolimus for the treatment of these patients from a Swedish healthcare system perspective.

Methods: Cost-effectiveness was assessed using a partitioned survival model consisting of three health states: progression-free survival (PFS), disease progression, and death. The proportion of patients in each state was calculated based on PFS and OS distributions from CheckMate 025. Average cost per state was estimated, and in combination with adverse events, subsequent treatment utilization, and drug costs, total model costs were calculated. Because CheckMate 025 allowed for treatment beyond progression, treatment costs were based on time to discontinuation (TTD) rather than PFS, reflecting a more conservative approach. Quality-adjusted life-years (QALYs) were calculated using quality of life assessments on EQ-5D and represented the effectiveness portion of the model. A lifetime perspective was applied (ie, 25 years) with costs and outcomes discounted by 5% annually. Sensitivity analyses were conducted to assess uncertainty.

Results: Nivolumab resulted in greater total costs versus everolimus (SEK 1,551,386 vs SEK 1,429,900, driven by differences in drug costs (SEK 939,416 vs SEK 294,050). Effectiveness (QALYs) was also greater for nivolumab (2.9 vs 2.2). The incremental cost-effectiveness ratio (ICER) was SEK 943,346 per QALY. Applying nivolumab costs based on PFS (vs TTD) to the model decreased costs to SEK 483,875 and reduced the ICER to SEK 705,215.

Conclusions: These analyses demonstrate that although treatment with nivolumab is associated with higher costs, nivolumab was cost-effective at established thresholds when accounting for treatment costs that continued through progression. We believe that this model structure could serve as a template for assessing cost-effectiveness in other European Union countries.

Clinical trial identification: NCT01668784

Legal entity responsible for the study: Sukhvinder Johal

Funding: Bristol-Myers Squibb

of continuous enrollment pre-index and no evidence of cystectomy were included. A subset of 5,531 (98.6%) had survival data available.

**Results:** The population was majority male (74%), with a mean age of 70. Among chemotherapy treated (T) patients (N = 3,750), the median number of days to tx initiation was 28.1, and among untreated (NT) patients (no therapy observed), the median follow-up was 218 days. NT compared to T patients, were older (72 vs 67) and had higher National Cancer Institute (NCI) comorbidity score (1 vs. 0.8). Among T patients, gemcitabine (GEM; 48%), carboplatin (CAR; 42%), cisplatin (CIS; 2%), and paclitaxel (PAC; 21%) were the 4 most common tx included in a first-line (1L) regimen. Patients treated with CIS were younger (62 vs 69 and 68) and healthier (NCI comorbidity score 0.7 vs. 1.1, and 1.0) vs. patients treated with CAR and other treatments (OT), respectively. Second-line (2L) tx was observed in 1,204 (13%) patients. A greater proportion of 1L CIS patients started 2L therapy (31%) vs. CAR (29%) and OT (18%). GEM (30%), CAR (30%) and PAC (30%) were the most common tx included in a 2L regimen. In the overall survival analysis, CAR patients have poorer survival than CIS or OT patients (median months from 1L initiation: 14.4 vs. 19.5 and 16.8, respectively; log rank p = 0.001).

**Conclusions:** The majority (60%) of mUC patients did not receive chemotherapy in this study. NT patients had characteristics similar to CAR patients, while those receiving CIS were younger, healthier, and had better outcomes. These findings provide further insight into treatment strategies in real world settings and highlight the unmet need in this patient population.

**Legal entity responsible for the study:** N/A

**Funding:** Genentech Inc.

**Disclosure:** E. Malagone-Monoaco, K. Wilson, H. Varker. Employee of Truven Health Analytics, Inc., which was paid by Genentech to conduct this study. S. Satnam-Hoang. Consultant to Genentech, which provided funding for this research. S. W. Lin, D. Taya, S. Ogale. Employed by Genentech and own Genentech/Roche stock.

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**Economic evaluation of pazopanib as first-line treatment of metastatic renal cell carcinoma in Greece**

A. Solakid1, G. Kourlaba1, L. Kontovinis2, E. Bourakis1, A. Boutis1, K. Koutsioukos1, J. Styris5, A. Tzounaris1, M. Chatzikok2, C. Michailid1, N. Maragkos1

**Health Economics, EVROSTON LP, Athens, Greece. 2Medical Oncology, Oncomedicare, Thessaloniki, Greece. 3Medical Oncology, Ateno Hospital, University of Athens, Athens, Greece. 41st Department of Clinical Oncology/Chemotherapy, Therission Cancer Hospital, Thessaloniki, Greece. 5Medical Oncology Unit, Department of Clinical Therapeutics, Alexandra Hospital, Athens, Greece. 6Medical Oncology, Hippokration General Hospital, Athens, Greece. 7Health Economics, Novartis Hellas, Athens, Greece. 8Health Economics, Novartis Hellas, Athens, Greece. 9Medical, Novartis Hellas, Athens, Greece, 10Health Services Organization and Management, National School of Public Health, Athens, Greece

**Background:** The NCNN Kidney Cancer Panel lists pazopanib and sunitinib as category 1 options for first-line treatment for stage IV renal cell carcinoma (RCC). The aim of this study was to evaluate the cost-effectiveness of pazopanib vs sunitinib as first-line treatment of metastatic RCC (mRCC) from a Greek third-party perspective.

**Methods:** A 3-state partitioned survival model was used. Estimates of progression free survival (PFS) and overall survival (OS) were from the COMPARZ trial. Utility values were based on adverse events in COMPARZ and EQ-5D values from the VIG1019512 trial. Cost inputs included drug acquisition and other treatment related costs including physician visits and lab and radiology tests. Resource use data were collected by DELPHI method from an expert panel of clinicians from private and public hospitals in Greece. A 5-year time horizon was used consistent with the maximum duration of follow-up in the analysis of OS in COMPARZ. The incremental cost-effectiveness ratio (ICER) was calculated. A threshold of €5,000 per QALY gained was used, per WHO Guidelines. Deterministic and probabilistic sensitivity analyses (DSA and PSA) were conducted.

**Results:** In the base case, pazopanib was less costly and more effective (“dominant”) compared with sunitinib, with €3,676 lower lifetime costs per patient and 0.058 greater discounted QALYs (€25,464 vs €28,140 and €1.16 vs 1.02). DSA and PSA suggest these results are robust. In DSA, pazopanib was dominant for different assumptions regarding PFS and utilities (Table). In 66% of PSA simulations, pazopanib was projected to yield more QALYs and lower costs vs sunitinib. The probability that pazopanib is cost-effective vs sunitinib was estimated to be 90% given the ICER threshold.

**Conclusions:** Pazopanib is likely to be dominant compared with sunitinib as first-line treatment of mRCC in the Greek healthcare setting.

**Table: 1034P**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Incremental Costs</th>
<th>Incremental QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICER initial estimate</td>
<td>€-3,676</td>
<td>0.058</td>
<td>Dominant</td>
</tr>
<tr>
<td>Investigator-assessed PFS</td>
<td>€-2,804</td>
<td>0.059</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

**Legal entity responsible for the study:** Dr. Georgia Kourlaba

**Funding:** Novartis Hellas

**Disclosure:** A. Solakid, G. Kourlaba. EVROSTON LP received funding from Novartis Hellas for this study. M. Chatziokou. Novartis employee. However, the study sponsor had no influence on the study design, data collection or writing of the abstract. C. Michailid. Novartis employee. However, the study sponsor had no influence on the study design, data collection or writing of the abstract. All other authors have declared no conflicts of interest.

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**Understanding real world treatment patterns, healthcare resource utilization (HRU) and costs among metastatic renal cell carcinoma (mRCC) patients**

R. Copher1, S. Dacosta Byfeito1, P. Buziniez2, S. Korrem2, M. Baig3


**Background:** Therapy targeting the vascular endothelial growth factor and mammalian target of rapamycin pathways are now the standard of care for patients (pts) with mRCC. However few studies have examined real-world treatment patterns and the impact on HRU and costs associated with these novel agents.

**Methods:** A retrospective study using a large, national US claims database from 7/2009-6/2015 was conducted. Commercially insured (COM) and Medicare Advantage (MA) newly diagnosed adult RCC pts (≥2 claims with ICD-9 189.0x) with ≥2 claims for metastases (metas) were identified. The first met claim date was the index date. Pts were required to be continuously enrolled (CE) in the health plan for 6m pre- and ≥1m post-index date and initiate systemic cancer therapy. Pts with other cancers or systemic cancer therapy in the baseline were excluded. Treatment patterns by line of therapy (LOT) were examined. A LOT started at the first date of cancer therapy and the regimen included all drugs received within 30 days. LOTs ended at the earliest of, start of a new drug, 260-day gap in initial regimen, death or CE-end. All-cause per pt per month (PPPM) HRU and costs (in US $) during LOT1, LOT2 and LOT3 by regimen were examined.

**Results:** There were 929 mRCC pts identified; 67% of pts were male. 47% were 65 yrs or age (mean age 63 and 57 yrs for MA pts vs. 63.5 CMU). Among all pts, 44% (n = 409) and 20% (n = 187) had a LOT2 and LOT3 during the study period. Mean total follow-up time was 17m, and mean duration of LOT1, LOT2 and LOT3 was 4.9, 4.6 and 4.2 m respectively. The most common regimens were sunitinib (42%), pazopanib (22%) and temsirolimus (16%) for LOT1, everolimus (24%), pazopanib (20%) and sunitinib (17%) for LOT2, and axitinib (24%), pazopanib (21%) and everolimus (17%) for LOT3. HRU, including inpatient stays (0.29, 0.24 and 0.26 PPPM for LOT1, LOT2 and LOT3), varied by regimen. Total PPPM costs were US$21,884, US$20,116 and US$21,173 for LOT1, LOT2 and LOT3 respectively by regimen.

**Conclusions:** With the emergence of new therapy options for mRCC, there is heterogeneity in treatment patterns with high associated HRU and costs. Future studies should examine optimal treatment sequencing.

**Legal entity responsible for the study:** Eisai, Inc and Optum

**Funding:** Eisai, Inc

**Disclosure:** R. Copher. Employment at Eisai, Inc Stock ownership (Eisai). S. Dacosta Byfeito, P. Buziniez: Employment with Optum. Optum received payment from Eisai, Inc to conduct the study being presented but employment is not dependent on Optum’s study with Eisai. Stock ownership (Optum/UnitedHealth). S. Korrem: Employment with Optum. Optum received payment from Eisai, Inc to conduct the study being presented but employment is not dependent on Optum’s study with Eisai. Stock ownership (Optum/UnitedHealth). M. Baig: Employment with Eisai, Inc.

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**A real-world study of patterns of Bacillus Calmette-Guerin (BCG) use and associated adverse events (AEs) in non-muscle invasive bladder cancer (NMIBC) patients in the United States**

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**Background:** Patterns of BCG use and associated AEs are not well understood. This study describes the demographic and clinical characteristics of NMIBC patients, and reports BCG-related AEs during BCG exposures.

**Methods:** This was a retrospective, observational cohort study of 59,955 patients from a U. S. insurance claims database between 1/1/2005-6/30/2015. Adult patients with ≥ 1 diagnosis code for bladder cancer (BC; ≥ 1 procedure code for transurethral resection (TUR; first TUR ≥ index date), ≥ 12 months of continuous enrollment pre-index; no evidence of BCG, chemotherapy, metastasis, or cystectomy pre-index; and no evidence of TUR in the 6-months pre-index were included. A total of 15,922 (27%) patients had BCG
Cancer-associated thrombosis (CAT) is a severe disease that requires special medical attention as about 10% of cancer patients die from thrombotic events. HRQL is often challenging when analysing the data. Not all events were captured in the planned HRQL assessments, which was a study limitation. Further work (possibly using qualitative methods) could help us to understand how and why patients’ HRQL is affected.

**Clinical trial identification:** NCT01130025

**Legal entity responsible for the study:** Leo Pharma A/S

**Funding:** Leo Pharma A/S

**Disclosure:** A.J. Lloyd: was paid a fixed fee for his work on the statistical analysis and report writing from this project S. Dewelde: was paid a fixed fee for her work analysing the data and supporting dissemination. E. Reimer: Employee of Leo Pharma A/S. A. Lee: Consultancy to Leo Pharma. Honararia from Pfizer, Bayer and research funding from Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

**Methods:** The observational, retrospective study of patients with CAT was based on national registry data from the Swedish National Board of Health and Welfare (NBHW). Persons diagnosed with cancer and thrombosis in 2012 were identified via ICD10 codes for cancer and venous thromboembolism (VTE) in the national patient register. Inpatient and specialized outpatient care resource utilization, along with data on pharmaceutical treatment and mortality in the study population, were elicited from the NBHW registries. Data was analysed for a 2-year period after each patient’s index date, i.e. after VTE diagnosis. Health care unit costs were collected from regional price lists and drug costs were extracted from the prescribed drugs registry.

**Results:** A total of 1,504 cases were identified in 2012 (mean age 69 years; 45% male) out of which 16% had lung cancer, 13% colorectal cancer, 9% breast cancer and 5% prostate cancer while the majority (57%) had other cancer types. The most common VTE diagnoses were pulmonary embolism (28%) and deep vein thrombosis (29%), and 19% had more than one thrombosis related diagnosis. On average, patients were hospitalized for total of 14 days and had 0.69 outpatient visits during the follow-up period. After 2 years, the morality rate was 68%. Cancer was reported as the main cause of death in most cases (91%). Pulmonary embolism was reported as a contributing factor in 17% of the deaths. The total cost of CAT during the 2 years was €14 million (€9400 per patient), out of which 88% were related to inpatient care. Among the four major cancer diagnoses, the cost of CAT per patient was highest for colorectal cancer (€9800) and lowest for breast cancer (€4700).

**Conclusions:** The trial data shows that experiencing rVTE or bleeding significantly worsens HRQL. The data allow us to quantify the burden for patients and the value of secondary VTE prevention. Detecting VTE related HRQL signals against the background of many other influences on HRQL measurement, proved to be a challenge when analysing the data. Not all events were captured in the planned HRQL assessments, which was a study limitation. Further work (possibly using qualitative methods) could help us to understand how and why patients’ HRQL is affected.

**Table: 1038P Estimated HRQL scores**

<table>
<thead>
<tr>
<th>Number of events</th>
<th>EQ-5D mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No event</td>
<td>4525</td>
<td>0.64</td>
</tr>
<tr>
<td>Non-fatal DVT</td>
<td>36</td>
<td>0.61</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>3</td>
<td>0.62</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>16</td>
<td>0.46</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>55</td>
<td>0.57</td>
</tr>
<tr>
<td>Major bleed</td>
<td>15</td>
<td>0.59</td>
</tr>
<tr>
<td>Non-major bleed</td>
<td>113</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Conclusions: CAT is associated with significant resource utilization and costs, out of which the largest portion is attributed to inpatient care.

Legal entity responsible for the study: The Swedish Institute for Health Economics

Funding: Leo Pharma AB

Disclosure: M.V. Holm: Employed at LEO Pharma AB, Sweden. All other authors have declared no conflicts of interest.

1041P  
Dalteparin vs. vitamin K antagonist (VKA) for the prevention of recurrent venous thromboembolism (VTE) in cancer patients with renal insufficiency: A patient level pharmacoeconomic analysis in four European countries

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Background: In a randomized trial (i.e. CLOT) which evaluated extended duration prophylaxis of recurrent VTE in cancer patients (Lee et al, 2003), dalteparin reduced the relative risk of recurrent VTE by 52% compared to oral VKA therapy (P = 0.002). A recent subgroup analysis in patients with moderate to severe renal impairment at randomization also revealed lower absolute VTE rates with dalteparin (3% vs. 17%; p = 0.011). A patient level pharmacoeconomic analysis was conducted to evaluate these indications from the French, Austrian and Dutch health care system perspectives.

Methods: Resource utilization data contained within the database was extracted and converted into direct cost estimates for each country. Univariate analysis was used to compare the total cost of therapy between patients randomized to dalteparin or VKA therapy for each country. To estimate the cost per quality adjusted life year (QALY) gained with dalteparin, health state utilities were measured in 24 members of the general public using the Time Trade-Off technique.

Results: When all of the cost components were combined for the entire population (n = 676), the dalteparin group had significantly higher mean overall costs than the VKA group in each of the respective countries (Table). However, the preference assessment revealed that 21 of 24 respondents (88%) selected dalteparin over VKA with an associated gain of 0.14 (95%CI: 0.10 – 0.18) QALYs, resulting in favourable cost effectiveness ratios.

Table: 1041P

<table>
<thead>
<tr>
<th>Country</th>
<th>Dalteparin</th>
<th>VKA</th>
<th>Cost / QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>€2,267 (80)</td>
<td>€1,352 (94)</td>
<td>€6,600</td>
</tr>
<tr>
<td>Austria</td>
<td>€2,687 (81)</td>
<td>€2,012 (102)</td>
<td>€4,900</td>
</tr>
<tr>
<td>Netherlands</td>
<td>€2,376 (81)</td>
<td>€1,724 (102)</td>
<td>€4,697</td>
</tr>
</tbody>
</table>

*p < 0.001; SE = standard error*The analysis in patients with renal impairment suggested an even better economic profile, with the cost per QALY gained being less than €4,000 in all three countries.

Conclusions: Extended duration prophylaxis with dalteparin is a clinically and cost effective alternative to VKA for the prevention of recurrent VTEs in patients with cancer, especially in those with renal impairment.

Legal entity responsible for the study: Pfizer Inc

Disclosure: L. Shane: Employed by the sponsor: Pfizer Inc. G. Dranitsaris: Consultant to Pfizer Inc. S. Woodruff, B. Valler, L. Burgers: Employed by Pfizer Inc. All other authors have declared no conflicts of interest.

1043P  
Modeling maintenance therapy in ovarian cancer

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Background: Maintenance therapy (MT) is a relatively new concept in the management of solid tumors, and it is difficult to determine how MT early in the treatment pathway may impact long-term outcomes. The objective of this study was to develop a model of the natural history of ovarian cancer (OC) and determine the impact of MT on overall survival and quality-adjusted life years (QALYs).

Methods: A microsimulation model was developed to allow patients to progress through therapy from first line to fifth, with MT following each of first-, second-, and third-line treatment. Progression was tracked using progression-free disease (PFS), treatment-free intervals (TFI), and survival in progressive disease. Overall survival is thus the accumulation of all survival in the model. Data to support the model were extracted from various sources describing studies in predominantly serious OC. PFS from a study of survival in 1,620 patients after initial platinum + taxane-based therapy; rates of discontinuing active therapy at each line, and rates and duration of chemotherapy, from a published survey of clinicians; and health state utility values from NICE Technology Appraisals for OC. Outcomes in the BCCA defined subgroups were estimated using hazard ratios from a meta-analysis and clinical trial.

Results: Simulations were run with n = 2,000 with stable results. In the absence of MT, life years (LYs) per patient were 1.11 and QALYs per patient were 0.69. Gains of 0.04 LYs and 0.05 QALYs were observed when MT was included after treatment for first, second, and third relapses; the TPI increased from 0.79 to 0.81 LYs and the chemotherapy-free interval increased by 0.09 LYs.

Conclusions: The model results are consistent with previous publications for OC, the impact of MT is demonstrated through delayed progression to subsequent therapy, longer treatment-free intervals, and sustained QALYs from delayed disease progression and fewer adverse events. Although the model was developed for subgroups of ovarian cancer (based on platinum sensitivity or BRCA status), data for these populations are limited. Further research, and more clinical trial or real-world data, are recommended to explore the impact of MT in subgroups.

Legal entity responsible for the study: PRMA Consulting Ltd

Funding: Tesaro Inc

Incremental cost-effectiveness analysis of hepatic metastasectomy in patients with advanced colon cancer and liver metastasis

S. Chainitikun  
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Background: Colorectal cancer with liver metastasis is a potentially curable malignancy. Multidisciplinary treatment including hepatic tumor resection provides 20–40% 5 year survival rate. However, the utility of hepatic resection for liver metastases in colorectal cancer is still debatable. Liver metastasectomy requires specialized centers having expertise, resources, and awareness which consume significant amount of hospital budgets. We aimed to evaluate the cost-effectiveness of hepatic metastasectomy in patients with advanced colon cancer with liver metastasis.

Methods: Medical records of advanced colon cancer patients with liver metastasis only who treated at the King Chulalongkorn Memorial Hospital during January 2007 to 31 December 2010 were reviewed. The study endpoint is to compare the cost per life-year gained in term of incremental cost-effectiveness ratio (ICER) between with or without hepatic metastasectomy by the decision model. Data regarding site of primary tumor, characteristics of liver metastases, treatment strategies, chemotherapy regimens, biologic agents, complications, health coverage and survival data were collected and analysed.

Results: There were 34 patients in liver surgery group and 28 patients in without surgery group. There was significantly longer median survival time in the surgery group vs no surgery, 42.2 vs 18.04 months, respectively (HR = 23.3, P < 0.001). Individual mean cost per patient was higher in the surgery group at 1,975,349 baht (60,446 USD)/case compared to no surgery group at 1,451,028 baht (44,402 USD)/case. The ICER of liver surgery over no surgery was 247,150 baht (7,563 USD) per life-year gained which is lower than the threshold derived from the national gross domestic product per capita.

Conclusions: Under the routine clinical service, hepatic metastasectomy is a cost-effective option for patients with colon cancer with liver only metastasis in the tertiary care hospital setting.

Legal entity responsible for the study: Medical Oncology Department, Faculty of Medicine, Chulalongkorn University

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

An Italian cost-effectiveness analysis of paclitaxel albumin (nab-paclitaxel) + gemcitabine vs gemcitabine alone for metastatic pancreatic cancer patients: The APICE study

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Background: In a Phase III clinical trial, nab-paclitaxel + gemcitabine (G) significantly improved overall survival, time to progression and response rate compared to G monotherapy in MP sails. The aim of APICE study was to evaluate the cost-effectiveness of nab-paclitaxel + G vs G in the treatment of MP patients in Italy.

Methods: A Markov model with four health states (progression-free, progressed, end of life and death) was developed to estimate costs, outcomes and quality-adjusted life-years (QALYs) over 4 years from the Italian National Health Service (INHS) perspective. Patients were assumed to receive G 100mg/m2 weekly or nab-paclitaxel 125mg/m2 + G 100mg/m2 weekly. Data on efficacy was derived from MPACT trial, while data on health care resource consumption was collected from a survey performed on nine Italian centres. Resources were valued at Euro (€) 2015. Published utility weights were applied to health states to estimate the impact of response, disease progression and adverse events on QALYs. Two sensitivity analyses tested the robustness of the base case incremental cost-effectiveness ratio (ICER).

Results: Compared to G in monotherapy, nab-paclitaxel + G gains an extra 0.154 QALYs (0.196 life-year saved) and incurs additional costs of €7888 per patient treated. This translates to an ICER of €46,022 (95%CI: €33,292; €78,960). One-way sensitivity analysis underscores ICER for nab-paclitaxel + G to be robust. Probabilistic sensitivity analysis highlighted that nab-paclitaxel has a 9.8 probability to be cost-effective for a threshold-value of €80,000 and is the optimal alternative from a threshold-value of €46,746 onwards.

Conclusions: Based on those findings, nab-paclitaxel + G can be considered cost-effective when compared to the informal acceptability threshold-value for ICER adopted for reimbursing other oncology drugs in Italy (€87,330, 95%CI: €37,024; €137,636).

Legal entity responsible for the study: Celgene Italia srl, Milan, Italy

Funding: Celgene Italia srl, Milan, Italy

Disclosure: All authors have declared no conflicts of interest.
immunotherapy of cancer

Baseline tumor T cell receptor (TcR) sequencing analysis and neo antigen load is associated with benefit in melanoma patients receiving sequential nivolumab and ipilimumab

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Background: In a randomized phase II clinical trial of nivolumab (NIVO) then ipilimumab (IPI) with a planned switch at week 12 (arm A), versus the reciprocal combination of IPI then NIVO (arm B), followed by maintenance NIVO in both arms, in 140 patients with metastatic unresectable melanoma, best overall response rates and overall survival were superior for arm A versus B (Weber, J et al Lancet Oncology, in press 2016), but grades 3-4 immune related side effects were similar.

Methods: In that trial, pre- and post-treatment tumors and peripheral blood samples were analyzed by DNA sequencing for TcR clonality and tumors were also analyzed for T cell infiltration. Whole exome sequencing was also performed to assess mutational and neo-epitope load in pre-treatment tumors.

Results: For 94 pre-treatment tumor samples, a combination of high T cell fraction and T cell clonality was associated with response to treatment in arm A (p = 0.019 using Fisher's exact test, odds ratio = 6.7), and with survival (p = 0.03) but not in arm B. In 22 paired samples, patients responding to treatment had an increase in the tumor T cell fraction and clonality post treatment at week 13 (p = 0.015 - signed ranked Wilcoxon test), but tumors from progressing patients had a decrease in T cell clonality compared to those responding to treatment (p = 0.008, U-test of pooled arms A and B). When changes in tumor T cell clonality and T cell fraction were assessed together at week 13, for both arms there was a strong correlation with response to treatment (p = 0.0023 with odds ratio of 30). Tumor mutational load was associated with response to NIVO then IPI in arm A (p = 0.03), but not with response to IPI then NIVO in arm B. In the peripheral blood, there were no differences in TcR clonality, or the abundance of the top TcR clone post-treatment compared to baseline. No peripheral blood pre-treatment TcR parameter was associated with response to treatment in either arm.

Conclusions: Baseline tumor micro-environment T cell infiltration and clonality are crucial determinants of response to treatment with the PD-1 blocking antibody nivolumab. Altering both parameters may impact on resistance to immunotherapy in melanoma.

Clinical trial identification: NCT01783938
Legal entity responsible for the study: BMS
Funding: BMS

Ongoing complete remissions in phase 1 of ZUMA-1: a phase 1-2 multi-center study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B cell non-Hodgkin lymphoma (NHL)

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Background: Diffuse large B-cell Lymphoma is 30%-58% of all NHL with an incidence of 3.8/100,000 in Europe (Tilly et al, Ann Oncol 2015). Therapy with CD28/CD3¿ anti-CD19 CAR T cells led to durable remissions in patients with relapsed/refractory B cell malignancies at the NCI (Kochenderfer, J Clin Oncol 2015). KTE-C19 utilizes the same CAR construct as the NCI trial but centrally manufactured in a streamlined 6- to 8-day process. We present updated ZUMA-1 phase 1 study data.

Methods: Patients received KTE-C19 at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg after cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) conditioning chemotherapy (Locke, ASH 2015). The primary objective was KTE-C19 safety. Secondary objectives included overall response rate (ORR), duration of response, and levels of blood CAR T cells and serum cytokines. Inclusion criteria were ECOG 0-1 and chemotherapy-refractory disease defined as progressive disease (PD) or stable disease as best response to last line of therapy, or PD ≤ 12 months after autologous stem cell transplant (ASCT).

Results: As of April 16, 2016, seven patients received KTE-C19. One patient had a dose-limiting toxicity (DLT) of grade 4 encephalopathy and cytokine release syndrome (CRS), and grade 5 intracranial hemorrhage unrelated to KTE-C19. Except for the patient with DLT, all grade 2-3 KTE-C19 related toxicity resolved. ORR was 71% (57% complete response [CR]). Three patients with PD within 6 months of ASCT have ongoing CR at 6-9+ months. CAR T cells peaked within two weeks and were detectable 1-6+ months post infusion. Updated results as of September 2016 including up to 1 year of follow up will be presented.

Conclusions: Ongoing CRs have been observed at 9+ months after a single KTE-C19 dose in patients with refractory aggressive NHL. CRS and neurotoxicity were self-limiting and generally reversible. The central manufacturing process and KTE-C19 regimen were deemed safe and feasible for further study. The ZUMA-1 phase 2 study (NCT02348216) is ongoing.

Clinical trial identification: NCT02348216
Legal entity responsible for the study: Kite Pharma
Funding: Kite Pharma

Changes in serum IL8 levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small cell lung cancer patients

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Background: Anti-PD-1 blockade effectively treats several tumor types. Yet, surrogate biomarkers of clinical benefit are needed to evaluate efficacy, given the delay in observing responses and the existence of pseudo-progressions. This work aims to
evaluate serum IL8 levels as a biomarker during anti-PD-1 mAb treatment of melanoma and non-small cell lung cancer (NSCLC) patients.

Methods: 44 metastatic melanoma and 19 metastatic NSCLC patients treated with anti-PD-1 mAb therapy as a single-agent, or in combination with anti-CTLA-4 mAb, were studied. Blood was withdrawn at baseline, 2-4 weeks after starting treatment, at best response and at disease progression. Serum IL8 levels were determined by sandwich ELISA. Wilcoxon test was used to compare changes in serum IL8 levels during treatment and the mean Whitney U test was used to assess strength of correlation between serum IL8 levels and clinical response assessed by RECIST 1.1 criteria.

Results: The discovery set consisted of 12 melanoma patients treated with anti-PD-1 mAbs. In responding patients, serum IL8 levels decreased significantly at the moment of BR compared to baseline levels, and significantly increased upon progression. In non-responders, IL8 levels significantly increased at the moment of progression compared to baseline levels (Table 1). These results were confirmed in a validation set of 17 melanoma and 19 NSCLC patients similarly treated with anti-PD-1 mAbs (Table 1). Additionally, we observed that early changes in serum IL8 levels (2-4 weeks after treatment initiation) strongly correlate with response in the melanoma discovery set (p < 0.05), melanoma validation set (p < 0.01), NSCLC set (p < 0.01) and in a group of 15 melanoma patients treated with anti-CTLA-4 in combination with anti-PD-1 mAbs (p < 0.001).

Conclusions: Changes in serum IL8 levels might be used to monitor and predict response to anti-PD-1 therapy in metastatic melanoma and NSCLC patients.

Legal entity responsible for the study: Clínica Universitaria de Navarra y Yale University

Funding: Gobierno de Navarra Salud, EU commission IACT and PROCRP, MINECO (SAF2008-03294, SAF2011-22851)

Disclosure: All authors have declared no conflicts of interest.

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### Table: 10550D

<table>
<thead>
<tr>
<th>Responders (clinical setting)</th>
<th>Baseline</th>
<th>Best response</th>
<th>Progression</th>
<th>Median IL8 level (pg/ml)</th>
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<tr>
<td>Melanoma (discovery set)</td>
<td>63.7 (60-69)</td>
<td>13.6 (5-19)</td>
<td>&lt;0.05</td>
<td>74.6 (20-138)</td>
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<tr>
<td>Melanoma (validation set)</td>
<td>116 (10-21)</td>
<td>49 (20-78)</td>
<td>&lt;0.05</td>
<td>249 (57-335)</td>
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<tr>
<td>NSCLC (discovery set)</td>
<td>15.3 (10-15)</td>
<td>13.7 (10-20)</td>
<td>&lt;0.05</td>
<td>237 (10-30)</td>
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<tr>
<td>NSCLC (clinical setting)</td>
<td>89 (33-190)</td>
<td>8 (3-15)</td>
<td>&lt;0.05</td>
<td>163 (50-40)</td>
</tr>
</tbody>
</table>

---

**Background:** Activating the immune system for therapeutic benefit in cancer has long been a goal in immunooncology. Combining a PD-L1 antagonist, durvalumab (D), with an antibody targeting a promising target for cancer treatment. MEDI0680 (M) is a humanized IgG4 mAb specific for human PD-1 that blocks interaction with PD-L1 and programmed cell death ligand-2 (PD-L2). Durvalumab (D), MEDI4736) is a selective, high-affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80. Blocking both the PD-1 receptor and its ligand by combining M + D offers the potential for complete PD-1/PD-L1 axis inhibition.

**Methods:** This ongoing Phase 1 open-label, dose-escalation and expansion study is complete PD-1/PD-L1 axis inhibition.

**Conclusions:** The MTD has not been reached. The most common drug-related AEs were pruritus (17%); diarrhea and fatigue (both 13%); and flushing, peripheral edema, and pyrexia (each 10%). Immune-related AEs were similar to those seen with other checkpoint blockade agents. No drug-related AEs led to death. 2 pts (7%) discontinued due to drug-related AEs. Of 26 evaluable pts, 1 had a complete response (CR; Cohort 5; bladder cancer), 3 had a partial response (PR) and 9 had stable disease (SD). Increased Ki67 (proliferating) CD4+ and CD8+ T-cells and elevated circulating IFNγ, CXCL9, CXCL10, and CXCL11 levels were observed with M + D, indicating pharmacodynamic activity of PD-1/PD-L1 pathway blockade. Updated clinical data will be presented.

---

**Table: 1050PD**

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<th>4</th>
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<td>5</td>
<td>3</td>
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<td>Patients with drug-related AEs, a (%)</td>
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<td>Grade 2</td>
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<td>33</td>
<td>20</td>
<td>33</td>
<td>23</td>
<td>20</td>
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<tr>
<td>Grade 3</td>
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<td>67</td>
<td>50</td>
<td>33</td>
<td>87</td>
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<tr>
<td>Grade 4</td>
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<td>M + D</td>
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<td>33</td>
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<td>33</td>
<td>20</td>
<td>33</td>
<td>23</td>
<td>20</td>
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<tr>
<td>Disease control (CR + PR + SD 6 weeks)</td>
<td>25</td>
<td>50</td>
<td>67</td>
<td>50</td>
<td>33</td>
<td>87</td>
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</tr>
</tbody>
</table>

**Disclosure:** All authors have declared no conflicts of interest.

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**Background:** The PD-1/PD-L1 pathway is a key regulator of T-cell activation and a promising target for cancer treatment. MEDI6060 (M) is a humanized IgG4 mAb specific for human PD-1 that blocks interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Durvalumab (D), MEDI4736) is a selective, high-affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80. Blocking both the PD-1 receptor and its ligand by combining M + D offers the potential for complete PD-1/PD-L1 axis inhibition.

**Methods:** This ongoing Phase 1 open-label, dose-escalation and expansion study is complete PD-1/PD-L1 axis inhibition.

**Conclusions:** The MTD has not been reached. The most common drug-related AEs were pruritus (17%), diarrhea and fatigue (both 13%), and flushing, peripheral edema, and pyrexia (each 10%). Immune-related AEs were similar to those seen with other checkpoint blockade agents. No drug-related AEs led to death. 2 pts (7%) discontinued due to drug-related AEs. Of 26 evaluable pts, 1 had a complete response (CR; Cohort 5; bladder cancer), 3 had a partial response (PR) and 9 had stable disease (SD). Increased Ki67 (proliferating) CD4+ and CD8+ T-cells and elevated circulating IFNγ, CXCL9, CXCL10, and CXCL11 levels were observed with M + D, indicating pharmacodynamic activity of PD-1/PD-L1 pathway blockade. Updated clinical data will be presented.

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Conclusions: M 10 mg/kg + D 10 mg/kg Q2W appears to be well-tolerated and active in this population. Clinical trial identification: NCT02118337
Legal entity responsible for the study: MedImmune
Funding: MedImmune
Disclosure: O. Hamad: Consulting/Advisory: Merck, Merck Serono, Pfizer, Amgen, Novartis, Roche, BMS, Genentech. In a phase 2, study, injection of advanced melanoma lesions with CV A21 resulted in increases in tumor immune-cell infiltration, up-regulation of γIFN response and immune-checkpoint molecule genes, including CD122 which may be a potential prognostic factor for anti-tumor activity by anti-CTLA-4 blockade strategies. Presented are the preliminary results of safety, tumor response, pharmacokinetics, and pharmacodynamics in the dose escalation phase.

Results: As of April 01 2016, 27 pts were treated (n = 7, 9, 7, 4 received 0.03, 0.1, 0.3, and 1 mg/kg MEDI0562, respectively). Adverse events (AEs) and treatment-related AEs were seen in 24 (88.9%) and 16 (59.3%) pts, respectively; the only related AE occurring in ≥10% of pts was fatigue (8/27, 29.6%). Most pts experienced AEs of Grade 1 and 2 in severity. Serious AEs (SAEs) were seen in 12 (44.4%) pts; no treatment-related or immune-related SAEs were observed. No related treatment discontinuations, deaths or dose limiting toxicities have occurred. Of 19 evaluable pts, 1 pt (0.03 mg/kg) with squamous cell carcinoma of the larynx had partial response at first tumor assessment and maintained for 3.7+ months (ongoing); 4 pts had stable disease. Serum exposure of MEDI0562 increased approximately dose proportionally. A 2-3-fold mean increase in peripheral Ki67+ CD4+ memory T cells was observed. Preclinical studies, OX40 agonists have been shown to stimulate immune effector and memory T cell function while attenuating immunosuppressive function of regulatory T cells, leading to anti-tumor activity. Methods: This is a Phase 1 study evaluating MEDI0562, a humanized OX40 agonist mAb, in adult pts with advanced solid tumors. The study has 2 phases: dose escalation and dose expansion. Dose escalation follows 3 + 3 design with pts enrolled in sequential cohorts of up to 6 dose levels of MEDI0562 (0.03, 0.1, 0.3, 1.0, 3.0, or 10 mg/kg, via intravenous infusion). Tumor assessments are performed every 8 weeks. Selected pts have mandatory pre- and on-treatment tumor biopsies to explore the relationship between drug exposure and pharmacodynamics. We report the preliminary results of safety, tumor response, pharmacokinetics, and pharmacodynamics in the dose escalation phase.

Conclusions: Preliminary data showed that MEDI0562 is generally well tolerated in adult pts with advanced solid tumors and exhibits clinical and pharmacological activity. A maximum tolerated dose has not been determined.

Clinical trial identification: NCT02318394
Legal entity responsible for the study: MedImmune LLC
Funding: MedImmune LLC

A first-in-human (FIH) study of PF-04518600 (PF-8600) OX40 agonist in adult patients (pts) with select advanced malignancies


1Cancer Center, MD Anderson Cancer Center, Houston, TX, USA, 2Clinical Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA, 3Medical Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands, 4Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, Netherlands, 5Medical Oncology, University of Washington Seattle Cancer Care Alliance, Seattle, WA, USA, 6Global R&D, Pfizer Inc., South San Francisco, CA, USA, 7Global R&D, Pfizer Inc., La Jolla, CA, USA, 8Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Background: Co-stimulation of activated T cells with agonistic monocolonal antibodies (mAb) against the tumor necrosis factor receptor superfamily member OX40 offers a novel immunotherapeutic approach to cancer. OX40 engagement may co-stimulate effector T cells and deplete regulatory T cells, resulting in enhanced tumor immunity. PF-8600 is a fully human agonist IgG2 mAb that targets OX40.

Methods: A Phase 1, open label, multicenter study is ongoing to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity of PF-8600 in pts with advanced melanoma, head and neck squamous cell, renal cell, or hepatocellular carcinoma. PF-8600 was administered intravenously at increasing doses (0.1 - 3 mg/kg) every 2 weeks until disease progression or unacceptable toxicity. Additional biomarker cohorts (opened at each dose level except 0.1 mg/kg) enrolled pts who consented to baseline and on-treatment tumor biopsy samples for immune profiling by immunohistochemistry and RNAseq.

Results: As of 09 MAR 2016, 31 pts have enrolled in the dose-escalation phase of PF-8600 study: 0.01 mg/kg (2 pts), 0.1 mg/kg (10 pts), 0.3 mg/kg (8 pts), 1.5 mg/kg (7 pts) and 3 mg/kg (4 pts). 25.8% of patients received ≥ 4 prior therapies for advanced disease. No dose limiting toxicities, no drug related or immune related grade (G) 3-5 adverse events (AEs) were observed. Drug-related AEs (DRAEs) were all G1/2 events and occurred in 21 pts (67.7%). The most common DRAEs were fatigue (29.0%) and decreased appetite (19.7%). Out of 25 pts evaluable for response, 1 pt experienced partial response (PR, -50%, confirmed), and 15 pts experienced stable disease (SD). 11 pts remain on treatment, and 5 patients continued treatment for >13 weeks. Assessment of peripheral blood lymphocyte indicated full OX40 receptor occupancy at ≥0.3 mg/kg, and maximal memory T cell proliferation at 0.1 and 0.3 mg/kg. Updated safety, antitumor activity, and biomarker data will be presented.

Conclusions: These preliminary results demonstrate that PF-8600 is safe up to 3 mg/kg. Updated safety, antitumor activity, and biomarker data will be presented.

Clinical trial identification: NCT02150666

Legal entity responsible for the study: Pfizer, Inc.

Funding: Pfizer, Inc.


1056PD Preventive dendritic cell vaccination in healthy Lynch syndrome mutation carriers


1Tumor Immunology and Medical Oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 2Tumor Immunology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 3Gastroenterology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 4Pharmacology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 5Dermatology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 6Human Genetics, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 7Pathology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 8Medical Oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands

Background: Lynch syndrome (LS) is an autosomal dominantly inherited syndrome caused by monoallelic germline aberrations affecting one of the DNA mismatch repair (MMR) genes. Defects in the DNA MMR pathway underlying the development of microsatellite instability in LS-associated cancer. The cumulative risk of colorectal cancer varies between 10-80% and is strongly associated with the causative germline defect. MMR deficiency in tumor DNA causes shifts in the translational reading frame resulting in the production of altered peptides, called neoepitopes. These are considered ‘foreign’ by the immune system. This was the rationale for a preventive neoantigen-based vaccination study with dendritic cells (DCs). DCs are the antigen-presenting cells of our immune system as a result of their naive T cell priming and T cell activation capabilities.

Methods: We recruited HLA-A*02:01 positive patients known to be a germline MMR-gene mutation carrier without signs of LS-associated disease or more than 5 years beyond detection of cancer. In the primary endpoint was to investigate the safety and feasibility of DC vaccinations. Secondary objectives were to evaluate whether monocytic-derived peptide-loaded DC can induce an immune response to the selected neoantigens (caspase-5 and TGF-BRI) and the tumor-associated antigen carcinoembryonic antigen (CEA).

Results: All patients (n = 20) were recruited within a year. DC vaccinations were on average well tolerated. No participants were hospitalized during study treatment. In all vaccinated mutation carriers flu-like symptoms occurred. In 17 of 20 patients an injection site reaction developed upon intradermal DC administration. One patient experienced grade 4 fever (>40 °C > 24 hours), as a result study treatment was discontinued. In all tested patients a cellular immune response against the control antigen was seen. Functional neoantigen- or CEA-specific T cells were shown in the challenged skin upon DC vaccination in 15 of 20 patients.

Conclusions: Preventive DC vaccination is feasible and safe in LS mutation carriers and functional neoantigen- and CEA-specific immune responses were shown. This study opens perspectives for future immunotherapy trials with the intention of cancer prevention.

Clinical trial identification: ClinicalTrials.gov NCT01885702

Legal entity responsible for the study: N/A

Funding: This work was supported by Grant 951.00.106 of the Netherlands Organization for Scientific Research (NWO), two Radboudumc Ph.D. grants and a Koninkin Wilhelmina Onderzoekspriis (KWO)-Grant KUN2009-4402 from the Dutch Cancer Society (KWF). CG Figdor is recipient of European Research Council (ERC)-Advanced grant PATHFINDER (269019) and a NWO Spinoza grant. IJM de Vries is recipient of NWO Vici Grant 918.14.655.
Background: There is increasing evidence that antibodies blocking the PD-1/PD-L1 checkpoint (either anti-PD-1 or anti-PD-L1) increase in-field anti-tumor responses to ionizing radiation and enhance abscopal effects on non-irradiated metastases. Here, we developed PET tracers based on therapeutic antibodies to visualize whole-body expression of the receptor/ligand pair of the important PD-1/PD-L1 checkpoint.

Methods: Mice bearing s.c. B16 melanomas were treated with therapeutic antibodies to PD-1 (in combination with CTLA-4 checkpoint blockade) or anti-PD-L1 alone. Immunomonitoring by Elispot shows increased INFg production by PBMC after vaccination site using cell encapsulation technology. This technology also enables whole-body pictures of imaging the expression of the receptor/ligand pair of the important PD-1/PD-L1 checkpoint.

Results: The newly developed PET tracers allowed high specificity and high-resolution imaging of PD-1 and PD-L1 expression. In addition, they permitted the non-invasive imaging of the distribution of the two therapeutic antibodies in both naive and tumor-bearing mice treated with hKET and CTLA-4 checkpoint blockade. Imaging of the respective knockout mice, blocking experiments with an excess amount of unlabeled antibodies, and the analysis of appearance of both wild-type B16 melanomas and PD-L1-CRISPR knockout melanomas demonstrated the high specificity of the two newly developed PET tracers. The in vivo imaging data were confirmed containing a clinically relevant adverse event was also possible.

Conclusions: In conclusion, we have developed two innovative PET tracers that allow imaging the expression of the receptor/ligand pair of the important PD-1/PD-L1 checkpoint and the biodistribution of surrogate checkpoint-blocking antibodies in fully immunocompetent mice. This technology also enables whole-body pictures of radiation/immunotherapy.

Legal entity responsible for the study: Animal care committee Freiburg

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
**Table 1060P**

<table>
<thead>
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<th>SPECIMEN TYPE</th>
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<th>Metastatic</th>
<th>Interstitial</th>
<th>Nontumorous</th>
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<td>1248</td>
<td>349 (28)</td>
<td>462 (36)</td>
<td>456 (35)</td>
<td>149 (11)</td>
</tr>
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</table>

Conclusions: This is one of the largest data sets of PD-L1 expression determined by an FDA-approved companion diagnostic in pts with advanced NSCLC screened for pembrolizumab therapy. 68% of pts with advanced NSCLC had PD-L1 TPS ≥1% and 28% had PD-L1 TPS ≥50%. The prevalence is similar across prior lines of therapy and different disease characteristics examined.


Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

**Methods:** Pts with mRCC were randomized to intravenous (IV) nivo 3 mg/kg + ipi 1 mg/kg (nivo3 + ipi1), nivo 1 mg/kg + ipi 3 mg/kg (nivo1 + ipi3), or nivo 3 mg/kg + ipi 3 mg/kg (nivo3 + ipi3) every 3 weeks for 4 doses, followed by nivo3 IV every 2 weeks until progression or toxicity. Key endpoints included safety, objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS).

**Results:** Both the nivo3 + ipi1 and nivo3 + ipi3 arms enrolled 47 pts, with median follow-up of 22 (range, 1–34) months (nivo3 + ipi3 arm [n = 6] discontinued due to toxicity). Baseline pt characteristics were generally balanced between the arms. Prior systemic therapy was administered in 47% and 55% in nivo3 + ipi1 and nivo3 + ipi3 arms, respectively. Grade 3–4 treatment-related adverse events (TRAEs) were reported in 38% (nivo3 + ipi1) and 62% (nivo3 + ipi3) of patients; of these, the most common were T lymphopenia (15% vs 28%), ALT (4% vs 21%), diarrhea (4% vs 15%), TAST (4% vs 13%), and colitis (0% vs 15%). The most common grade 3–4 select TRAEs were gastrointestinal (4% vs 23%) and hepatic (6% vs 21%). Efficacy is summarized in the table.

**Conclusions:** Almost 2 years of follow-up of patients with mRCC treated with nivo + ipi shows manageable safety as observed previously, high ORR and durable responses with promising OS. Ipi showed dose-related toxicity, which further supports development of nivo + ipi1 in the first-line setting.

**Table: 1062P**

<table>
<thead>
<tr>
<th></th>
<th>Nivo3 + ipi1</th>
<th>Nivo3 + ipi3</th>
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<tr>
<td>ORR, n (%)</td>
<td>19 (40)</td>
<td>19 (40)</td>
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<tr>
<td>Median DOR, mos (range)</td>
<td>20.4 (2.1–32.2+)</td>
<td>19.7 (2.8–31.7+)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>19 (40)</td>
<td>17 (36)</td>
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<td>Progressive disease, n (%)</td>
<td>8 (17)</td>
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<td>Median OS, mos (range)</td>
<td>Not reached (3.5–34.5+)</td>
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<tr>
<td>Median PFS, mos (range)</td>
<td>6.6 (1.1–33.7+)</td>
<td>9.1 (1.0–33.1+)</td>
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<td><strong>ii = censored</strong></td>
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**Clinical trial identification:** NCT01472081

**Legal entity responsible for the study:** Bristol-Myers Squibb

**Funding:** Bristol-Myers Squibb


**Background:** The ability of Vγ9+ γδ T cells to target cancer cells via recognition of phosphoantigens has resulted in treatments such as ImmunCell®, which is currently being evaluated in an adaptive phase II/III study. In addition, we have developed γδ T cells expressing chimeric antigen receptors (CARs) to maximise the therapeutic potential of both γδ T cell and CAR-T therapy. We rationally designed a CAR construct that takes advantage of the defined antigen specificity of Vγ9+ γδ T cells resulting in a potential cellular therapy with enhanced effector functions whilst minimising ‘on-target, off-tumour’ side effects.

**Methods:** A CD19 targeting CAR was designed comprising costimulatory domains from CD28 and CD137 (signal-2). This design was tested against a classical CAR, comprising the aforementioned costimulatory domains plus a ‘signal-1’ providing CD3xi activation domain. Vγ9+ γδ T cells from healthy individuals were expanded in culture, and CAR expression achieved by lentiviral transduction. Ability of transduced γδ T cells to target CD19+ cancer cell lines, RAMOS and DAUDI, was assessed using a flow cytometry based cytotoxicity assay.

**Results:** γδ T cells were successfully transduced with both CAR constructs, these were discriminated by qPCR using two primer sets. γδ T cells transduced with either construct exhibited increased cytotoxicity against the CD19+ DAUDI and RAMOS target cells. Strikingly, a 3-fold increase in cytotoxicity was measured against RAMOS cells, which usually display low sensitivity to unmodified γδ T cell-mediated killing.

**Conclusions:** We have demonstrated a novel γδ specific CAR design that does not require incorporation of a CD3xi signalling domain to elicit effector function ‘signal-1’ is provided by the γδ T cell receptor (TCR) resulting in a TCR-tunable CAR construct. As healthy cells do not accumulate phosphoantigens, this CAR design should only elicit effector function against cancer cells, reducing ‘on-target, off-tumour’ side effects – a major safety concern. Moreover, CAR expressing γδ T cells may result in a potent targeted treatment, as both phosphoantigen and the CAR target contribute to identification and killing of cancerous cells in vivo.

**Legal entity responsible for the study:** TC BioPharm Limited

**Funding:** TC BioPharm Limited

**Disclosure:** M.D. Leek: Founder and employee of the presenting institution – TC BioPharm. A. Patakas, A. Hannigan, D. Paruzina: Employee of the institution submitting this abstract.
Background: Adoptive cell therapy (ACT) with tumor infiltrating lymphocytes (TILs) is based on the infusion of T cells isolated and expanded from tumor lesions of the individual patients. This treatment can induce unprecedented rates of durable complete responses in metastatic melanoma. The aim of this study was to characterize TILs from primary renal cell carcinoma (RCC), in order to initiate a clinical trial testing TIL therapy for patients with RCC. Preliminary data on TIL expansion were previously presented at ESMO Symposium on Immuno-Oncology 2015 (1). Here, final results of expansion, functional characterization and comparison with T cell responses in melanoma are presented.

Methods: Primary tumor lesions from 25 patients with RCC, scheduled for radical or partial nephrectomy were collected. TIL were isolated and expanded from tumor fragments with standard methods derived from clinical trials of melanoma. Autologous tumor cell lines were established from the same lesions and used as killing-targels for TIL.

Results: TIL cultures from primary RCC were successfully generated and expanded to clinical numbers from 23 of 25 (92%) samples. Expanded TIL showed phenotypic characteristics similar to melanoma, with >95% CD3+ T cells and a considerably variable CD4/CD8 ratio. CD8+ T cell responses against autologous tumor cell lines were detected in 11 of 15 RCC patients (73%) where an autologous RCC cell line was available. Tumoralucial capacity was confirmed by cytotoxicity assays. However, both frequency and magnitude of CD8+ T cell responses were generally higher in melanoma. Multidimensional characterization of three types of functional T cell responses revealed a unique pattern of anti-tumor reactivity of RCC-TIL compared to melanoma.

Conclusions: TILs from RCC-specimens can be isolated and expanded to clinical numbers. Tumor-recognition in vitro can be demonstrated for the majority of samples. However, immune responses of expanded CD8+ TILs from RCC are on average weaker than in melanoma and display a unique functional pattern, typical of heavily exhausted immune cells. 1) Andersen R. et al. Preclinical development of adoptive cell therapy with tumor-infiltrating lymphocytes for patients with renal cell carcinoma. Annals of Oncology 2015 (3). Here, final results of expansion, functional characterization and comparison with T cell responses in melanoma are presented.

Disclosure: All authors have declared no conflicts of interest.

Funding: None

Legal entity responsible for the study: N/A

References:
2.Disclosure: All authors have declared no conflicts of interest.

Funding: None

Legal entity responsible for the study: N/A

References:
2. Disclosure: All authors have declared no conflicts of interest.

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2. Disclosure: All authors have declared no conflicts of interest.

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Legal entity responsible for the study: N/A

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2. Disclosure: All authors have declared no conflicts of interest.

Funding: None

Legal entity responsible for the study: N/A

References:
2. Disclosure: All authors have declared no conflicts of interest.

Funding: None

Legal entity responsible for the study: N/A

References:
2. Disclosure: All authors have declared no conflicts of interest.

Funding: None

Legal entity responsible for the study: N/A

References:
Adenosine A2A receptor antagonist, CPI-444, blocks adenosine-mediated T cell suppression and exhibits anti-tumor activity alone and in combination with anti-PD-1 and anti-PD-L1

S. Willingham1, P. Ho1, R. Leone2, G. Choy1, J. Powell1, I. McCaffrey1, R. Miller2, S. Willingham1

1Translational Sciences, Corvus Pharmaceuticals, Burlingame, CA, USA, 2Department of Oncology, Johns Hopkins University, Baltimore, MD, USA, 3Clinical Development, Corvus Pharmaceuticals, Burlingame, CA, USA

Background: Elevated extracellular adenosine in the tumor microenvironment generates an immunosuppressive niche that promotes tumor growth and metastasis. Adenosine signaling via A2A receptor (A2AR) on immune cells suppresses anti-tumor immunity and may also limit efficacy of immunotherapies such as anti-PD-1 and anti-PD-L1 antibodies.

Methods: CPI-444 is a potent, oral, selective A2AR antagonist that has been well tolerated in phase 1 and 2 studies in non-oncology indications. The efficacy of CPI-444 ± anti-PD-1-L1 or anti-PD-1-L1 was evaluated in MC38 and CT26 syngeneic mouse tumor models.

Results: In MC38, daily treatment of mice with CPI-444 (1, 10, 100 mg/kg) led to dose-dependent inhibition of tumor growth, leading to tumor elimination in 9/30 mice. Combining CPI-444 with anti-PD-L1 treatment in MC38 synergistically inhibited tumor growth and eliminated tumors in 90% of treated mice. In an additional model, CT26, CPI-444 alone or anti-PD-1 alone led to non-significant reductions in tumor growth; however, the combination of CPI-444 and anti-PD-1 led to a synergistic inhibition of tumor growth and prolonged survival compared to either agent alone. When cured mice were later re-challenged with MC38 cells, tumor growth was fully inhibited, indicating that CPI-444 induced systemic anti-tumor immune memory. CD8+ T cell depletion abrogated the efficacy of CPI-444 ± anti-PD-L1 treatment, demonstrating a role for CD8+ T cells in mediating primary and secondary immune responses.

Conclusions: Based on these results and others, we have initiated a Phase 1b clinical trial to examine safety, tolerability, biomarkers, and preliminary efficacy of CPI-444 as a single agent and in combination in the investigational anti-PD-L1 antibody, nivolumab, in patients at high risk for recurrence. Clinical trial identification: NCT02655822

Legal entity responsible for the study: Corvus Pharmaceuticals


Interim survival analysis of a phase II trial combining trastuzumab and NeuVax, a HER2-targeted peptide vaccine, to prevent breast cancer recurrence in HER2 low expression

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Background: The HER2-targeted monoclonal antibody, trastuzumab (Tz), is standard of care (SOC) for breast cancer (BCa) patients (pts) with HER2-over-expressing (IHC 3+, OE) tumors and reduces recurrence by 50%. Tz may also have some efficacy in HER2 1-2+ by IHC (low expression, LE), but it is not currently approved for these pts. LE pts are at increased risk for recurrence. We have previously shown that NeuVax (E75 peptide + GM-CSF), a HER2-targeted cancer vaccine, is safe, immunogenic, and has clinical activity, particularly in LE pts. We are conducting a phase II trial combining Tz and NeuVax to prevent BCa recurrence in HER2 LE pts. Given the known cardiac toxicity (txn) of Tz, there is concern that combination therapy may worsen this txn. Here, we present the interim safety data.

Methods: Disease-free, HLA-A2, A3, A24, or A26+, HER2 LE pts at high risk for recurrence were enrolled after SOC treatment and randomized to vaccine group (VG) receiving Tz and NeuVax or control group (CG) receiving Tz and GM-CSF only. Cardiac ejection fraction (EF) was assessed at baseline and serially throughout treatment. Tz dosing was 8mg/kg loading, then 6mg/kg every 3 weeks. Pts received 6 total inoculations of NeuVax or GM-CSF, one every 3 weeks starting with the third Tz infusion. Demographic and safety data were collected and analyzed with appropriate statistical tests.

Results: In March 2016, the 150th pt was randomized triggering this pre-specified safety analysis (VG n = 81, CG n = 69). There were no significant differences in treatment factors. There were no related toxicity grade 3 nor difference between treatment arms. There was no difference in EF over time (baseline (BG) to 6mo (6M)) between VG (TG 61.4 ± 8.6%, TL 60.5 ± 9.8%* p = 0.16, TL 60.7 ± 9.4%, p = 0.78). There was 1 CG pt who experienced a grade 3 cardiac adverse event, but their EF returned to baseline after discontinuation of Tz.

Conclusions: This novel combination of Tz and NeuVax in HER2 LE pts is well tolerated and the cardiac effects of Tz are not impacted by the addition of NeuVax. We will continue to enroll in this ongoing trial, and will report immunologic and clinical outcomes in a planned interim analysis after 12 months follow-up.

Clinical trial identification: NCT01955152

Legal entity responsible for the study: N/A

Funding: Galena Biopharma


Consultant for Galena Biopharma. All other authors have declared no conflicts of interest.

Impact of non-proportionality of hazards on time-to-event endpoints with nivolumab: Re-analysis of melanoma and NSCLC pivotal trials

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Background: Immunotherapy could become the standard treatment in many cancers in the near future. Treatment effects on time-to-event endpoints are described by proportional-hazards models (PH). PH assumption leads to powerful tests when correct but in the context of IT, it can be poor, leading to significant power losses. More, non-PH models work poorly in IT situations and require some knowledge of the form of non-PH which is not available. We propose a method that works well in both situations applicable to IT.

Methods: Data from nivolumab pivotal clinical trials (melanoma: NCT01721772, NSCLC: NCT01642004) were analyzed to investigate the impact of non-PH on OS. These studies relied on a hypothesis of PH situation but did not investigate the impact of its possible violation on final results. We used a general multivariate non-PH model in which very broad families of situations can be described. This allowed construction of a test based on integrated Brownian motion (O’Quigley 2003).

Results: Melanoma trial exhibited PH whereas NSCLC did not. Our test was applied in both trials and exhibited an almost identical power to that of the log-rank test under PH situations but had typically much greater power under non-PH situations. For the NSCLC data, the test showed the data to be well modeled by a PH model (p < 0.001) was obtained with both tests. For the melanoma data, p-value for our test was more powerful that the log-rank test (p < 0.001) due to non-PH behavior of data. Nevertheless, nivolumab effect in melanoma was strong enough to compensate for non-PH effect.

Conclusions: Immunotherapy survival curves exhibit peculiarities which may violate the underlying PH assumption. We analyzed nivolumab pivotal trials for OS and demonstrated usefulness of our test. This may be suitable for any condition encountered in immunotherapy trials and is not dependent on any PH assumption.

Legal entity responsible for the study: ARTIC

Funding: ARTIC

Disclosure: All authors have declared no conflicts of interest.

A phase I dose escalation trial to assess the safety and preliminary efficacy of mFOLFOX6 combined with pembrolizumab (MK3475) in advanced gastrointestinal malignancies


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Background: Combining chemotherapy with immune checkpoint inhibitors may have additive or synergistic clinical activity. The objective of this phase I trial was to assess safety and dose limiting toxicities (DLTs) of combining mFOLFOX6 and pembrolizumab in advanced gastrointestinal (GI) malignancies.

Methods: This phase I trial used a 3 × 3 dose escalation design and included patients with chemotherapy-refractory advanced GI malignancies for which FOLFOX is indicated. Study treatment consisted of a phased regimen with patients receiving two cycles of mFOLFOX6 every 2 weeks followed by subsequent treatments with mFOLFOX6 plus pembrolizumab (75mg or 200mg) IV every 2 weeks. A DLT was considered if there was at least a possible causal relationship to pembrolizumab or the combination and occurred in

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A Phase 1 first-in-human study of MEDI0680, an anti-PD-1 monoclonal antibody (mAb) in adult patients (pts) with advanced tumors

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Background: Programmed cell death-1 (PD-1) inhibits T-cell activation. Blocking the PD-1/PD-L1 axis has an acceptable safety profile, induces antitumor responses, and provides clinical benefit across tumors. MEDI0680 is a humanized IgG4 mAb specific for human PD-1 that blocks interaction with PD-L1/2.

Methods: This is an ongoing Phase 1, multicenter, open-label, first-in-human, dose-escalation and expansion study of single-agent MEDI0680 in immunotherapy-naive pts with advanced solid tumors. Primary objectives are safety/ tolerability and maximum tolerated dose (MTD). Secondary objectives include pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity (modified RECIST v1.1).

Results: As of 2 November 2018, 58 pts have enrolled across 9 cohorts (0.1-20 mg/kg given Q3W, Q2W, QWx2 then Q2W, or QWx4 then Q2W, related Grade 3/4 AEs occurred in 10 pts; most common (>1 pt) were anemia, arthralgia and increased AST (3% each). 2 pts discontinued due to related AEs: pyrexia in 1 pt, and increased AST, myositis and myoglobinuria in 1 pt. There were no Grade 5 related AEs. MEDI0680 had a linear PK profile with dose-proportional increases in peak serum concentration. Median PD-1 receptor occupancy on CD3+ T cells was >70% after 1 cycle of 10 or 20 mg/kg Q2W. Increased percentages of CD8+ / CD30+ and HLA-DR+ T cells; increased levels of plasma IFNγ; and enhanced intra-tumor gene expression for these factors were seen after treatment, demonstrating biological activity of MEDI0680. Of 51 evaluable pts, 9 (18%) had an objective response (8 had renal cancer or melanoma), including 1 (2%) complete response (renal cancer). 14 (28%) pts had stable disease as their best response, 4 (7%) had partial response, 4 (7%) had progressive disease; biomarker assessments will be presented.

Conclusions: MEDI0680 has an acceptable safety profile, induces antitumor responses, and provides clinical benefit across tumors. The combination of mFOLFOX6 with pembrolizumab (200 mg IV every 2 weeks) has an acceptable safety profile. Further assessment of safety and efficacy is being evaluated in phase II dose-expansion cohorts.
myeloid-derived suppressor cells (MDSC), regulatory T cells, M2 macrophages, and stimulates the production of immunosuppressive cytokines. PS-targeting antibodies have significant anti-tumor effects in multiple preclinical tumor models to re-activate the immune response in the tumor microenvironment.

**Methods:** The combination of PS-targeting antibody ch1N11 with anti-PD-1 or anti-PD-L1 antibodies was compared to single agent therapy in E0771 and EMT-6 mouse syngeneic breast tumor models. Mice were treated IP up to twice per week with ch1N11, anti-PD-1, or anti-PD-L1 as single agents or combinations of antibodies. Tumor and spleen tissue were analyzed by FACS, ELISPOT, immunohistochemistry and RNA expression profiling.

**Results:** In both tumor models examined, the anti-tumor effect of ch1N11 with combination therapy was significantly superior to single agent therapy. Combination therapy of ch1N11 with anti-PD-1 or anti-PD-L1 significantly inhibited tumor growth by over 90% with greater complete tumor regression compared to single agent therapy in E0771 tumors. Furthermore, combination treatment induced greater rejection of tumors upon tumor re-challenge. Analysis of the tumor microenvironment indicated that the combination of antibody-mediated blockade of PS and PD-1 significantly enhanced tumor infiltration by CD8+ T cells, up regulation of immune activation genes and a decrease in tumor promoting genes.

**Conclusions:** These results support the combination of PS-targeting antibodies with anti-PD-1 or anti-PD-L1 antibodies for immunotherapy of cancer, including breast cancer.

**Legal entity responsible for the study:** Peregrine Pharmaceuticals

**Funding:** Peregrine Pharmaceuticals

**Disclosure:** J. Hutchins: I am an employee of Peregrine Pharmaceuticals. J. Wu: I am an employee of Peregrine Pharmaceuticals. Funding: Peregrine Pharmaceuticals

**Legal entity responsible for the study:** Adaptimmune LLC

**Disclosure:** C. Mackal, S. D’Angelo, S. Grupp, J. Geng, M. Drutz, W. Chow, K. Chagin, M. Mierla, G. Karup, T. Trivedi, T. Holdich, L. Pandite, R. Amado

<table>
<thead>
<tr>
<th>Cohort</th>
<th>NY-ESO-1 expression</th>
<th>Lymphodepleting Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>high</td>
<td>Fludarabine (FL) 30 mg/m2/day x 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclophosphamide (CTX) 1800 mg/m2/day x 2</td>
</tr>
<tr>
<td>2</td>
<td>low</td>
<td>B. CTX 1800 mg/m2/day x 2</td>
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<tr>
<td>3</td>
<td>high</td>
<td>C. FL 30 mg/m2/day x 3, CTX 600 mg/m2/day x 3</td>
</tr>
<tr>
<td>4 (to open if not effective)</td>
<td>high</td>
<td>moderate</td>
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**Results:** Enrollment in cohort 1 is complete (12 pts), ongoing in cohorts 2 and 3 (2 in each). ORR in cohort 1 is 50% (95% 38-62). Two pts receiving non target doses (<1 x 10^7 transduced T-cells) did not respond. Excluding these, the ORR is 60%. The median DOIR was 51.5 weeks (max of 77.3 weeks). The most common treatment-emergent AEs reported in all cohorts are fatigue, lymphopenia (94% each), neutropenia (88%), anemia (81%), nausea (81%), thrombocytopenia (88%) as of January 2016. Six events of CRS were reported; all resolved with supportive therapy. One fatal SAE (BM failure occurred) in Cohort 2.

**Conclusions:** The NY-ESO-1259 SPEAR T-cells™ have promising efficacy and acceptable safety profile in pts with SS who highly express NY-ESO. Efficacy and safety data will be further evaluated and presented from subjects enrolled in all cohorts.

**Clinical trial identification:** NCT01343043

**Legal entity responsible for the study:** Adaptimmune LLC

**Funding:** Adaptimmune LLC

**Disclosure:** K. Chagin, M. Mehler, G. Kari, T. Trivedi, T. Holdich, R. Amado. Author is an employee of Adaptimmune. L. Pandite is an employee of Adaptimmune. All other authors have declared no conflicts of interest.

**1075P** Open label non-randomized multi-cohort pilot study of genetically engineered NY-ESO-1 specific NY-ESO-1c259 SPEAR T-cells™ in HLA-A*0201 patients with synovial sarcoma (NCT01343043)

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**Background:** NY-ESO-1, a member of the cancer-testis family of tumor antigens, is expressed in ~70% of Synovial Sarcoma (SS) cases. NY-ESO-1c259 SPEAR T-cells™ recognizing the NY-ESO-1 derived SLLMVTTTC peptide complexed with HLA-A*02 have been developed for study in SS.

**Methods:** The primary endpoint of overall response rate (ORR (CR + PR)) will be evaluated in high NY-ESO expressors [2 + , 3+ NY-ESO in ≥ 50% of tumor cells by IHC (Cohorts 1, 3, and 4)] and low expressers [1+ in >1%, 2 + , 3+ in <50% (Cohort 2)] in the context of different lymphodepleting regimens (Table). Secondary endpoints include safety, duration of response (DOR), PFS, OS, and persistence of gene-marked cells. Subjects are HLA-A*0201, 05 or 06, with unresectable, metastatic or recurrent SS expressing NY-ESO-1, failed at least one regimen of ifosfamide and/or doxorubicin. Eligible subjects are leukapheresed; T-cells are isolated, activated, transduced and expanded. Target dose is ≤1 x 10^10 to ≤6 x 10^10 transduced T-cells. Disease assessments (RECIST v1.1) occur at weeks 4, 8 and 12 post T-cell infusion, and every three months thereafter.

**Conclusions:** Our study shows that 20% of SAs are MSI and 80% of these have a high expression of PDL1. This makes these cases an ideal candidate for immune checkpoint inhibitor therapies targeting PDL1.

**Legal entity responsible for the study:** Queen’s University Belfast

**Funding:** Cancer Research UK, Experimental Cancer Medicine Centre Network, Sean Cranmore Memorial Fund, Tom Simms Memorial Fund, Friends of the Cancer Centre and HSC Public Health Agency

**Disclosure:** All authors have declared no conflicts of interest.

**1076P** Microsatellite instability and PDL1 expression in small bowel adenocarcinoma - potential for immune checkpoint Inhibitor therapies

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**Background:** Small bowel adenocarcinoma (SBA) is a rare disease but incidence rates are on the rise. Management of SBA is challenging as there is a dearth of known molecular markers and the role and type of adjuvant chemotherapy is also not well defined. Expression of PDL1 in microsatellite instable (MSI) colorectal cancer makes an attractive target for immune checkpoint inhibitor therapies. In this study we have tested this hypothesis in SBA.

**Methods:** Using a retrospective 28 patient matched normal-tumour cohort we investigated MSI using a PCR assay looking at five mononucleotide repeat markers (BAT-25, BAT-26, NR-21, NR-24 and M0N0-27). MSI was called where three or more markers were affected. PDL1 immunohistochemistry was carried out on a Ventana Benchmark XT platform using PD-L1/CD274 (SP142) antibody at 1:4 dilution. Scoring was done separately for epithelial tumour cells along the invasive front, peritumoral lymphoid follicles and intra-tumoral lymphoid cells using four grades: negative (for no staining), low, moderate and high.

**Results:** Six cases were identified to be MSI. As shown in Table 1 out of these we observed five to have a high PDL1 expression in both peritumoral lymphoid follicles and epithelial tumour cells along the invasive front. We observed low PDL1 expression in intra-tumoral lymphoid cells in all samples.

**1077P** A meta-analysis of immune-related adverse events (irAE) of Immune checkpoint inhibitors (ICI) from cancer clinical trials

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**Background:** Targeting immune checkpoints is a novel and growing strategic approach in cancer therapy. This strategy may trigger irAE. We hypothesize that more patients (pts) will develop irAE with ICI targeting only immune cells compared to ICI targeting tumor cells as well (PD-L1). In addition, we want to determine specific irAE profile and overall response rate (ORR) for each of the ICIs by target(s).
Methods: We reviewed all ICJ cancer clinical trials (103, 201 arms) that reported irAE and were published on PubMed or presented at an ASCO meeting (only if not published on PubMed) during 2005–2015. 127 arms from 81 trials were eligible for this meta-analysis (1409 pts). We collected and compared arm-specific data including ICJ target, number of pts with irAE any grade, 3+ and grade 5, specific irAE, and ORR. P package “meta” was used for the meta-analysis and calculate and compare % of pts with irAE and ORR.

Results: 23 studies with 2392 pts from 34 arms treated with ICJ reported the incidence (%) of patients with any grade irAE per immune checkpoint target inhibition. The majority of arms (91%) and pts (88%) studied were on phase 1/2 clinical trials. Pts were treated for solid malignancy on 33 arms (97%), mainly melanoma (44.1%). No arms included ICJ combination. Incidence (%) of pts with irAE any grade was higher with ICJ targeting CTLA-4 (54%) and PD-1 (26%) and PD-L1 ICJ (13.7%) (P < 0.001). % pts with irAE grade 3+ was higher with ICJ targeting CTLA-4 (19%) than ICJ targeting PD-1 or PD-L1 (P < 0.001). irAE grade 5 was not significantly different among different ICJ (<1%).

Conclusions: Our meta-analysis supported our mechanistic-driven hypothesis that ICJ targeting only immune cells caused more pts to develop irAE. Most specific irAE % and ORR were highest with PD-1/CTLA-4 ICJ combination. Our observation is important to guide designing future ICJ combination clinical trials. We encourage investigators to report % pts with global irAE in ICJ trials.

Legal entity responsible for the study: Georgia Cancer Center at Augusta University

Funding: Georgia Cancer Center at Augusta University

Disclosure: All authors have declared no conflicts of interest.

1078P

Combining complementary mechanisms of immune activation: NKTR-214, a biased IL-2 pathway agonist and immune checkpoint antagonists


Research Biology, Nektar Therapeutics, San Francisco, CA, USA

Background: NKTR-214 is an agonist of the IL-2 pathway that provides a biased, sustained stimulation of the IL-2Rγc complex resulting in expansion of CD8(+)/T cells compared to regulatory T cells in the tumor. (1) NKTR-214 is currently in an outpatient Phase 1 clinical trial to evaluate MTX, pharmacokinetics, pharmacodynamics, and mechanism in solid tumors. Here we describe T-cell clonality and formation of tumor-reactive immune memory after administering NKTR-214 and checkpoint inhibitor antibodies in murine tumor models.

Methods: Mice bearing subcutaneous established EMT6 breast or CT26 colon tumors were treated with single agent NKTR-214 (pH4), murine anti-CTLA4 or anti-PD1 (twice weekly), or their combinations. Anti-tumor memory was assessed by 1) rechallenging tumor-free mice and 2) transferring splenocytes from tumor-free animals into tumor-bearing recipients. Immune cell enumeration used flow cytometry; T-cell clonality used the ImmunoSEQ platform (Adaptive Biotechnologies).

Results: While EMT6 and CT26 were refractory to single agent regimens, NKTR-214 achieved synergistic anti-tumor activity with antiPD1 or anti-CTLA4 superior to both antibodies combined. Tumor rechallenge demonstrated anti-tumor memory was durable, specific, and marked by vigorous proliferative memory T cells. The two antibodies produced significant increases in T cell density but modest increases in T cell clonality. In contrast, when NKTR-214 combined with either checkpoint antibody, a greater increase in both T cell density and clonality was observed.

Conclusions: NKTR-214 delivers a long-lived, biased activation of the potent IL-2 pathway, favorable pharmacokinetics and mechanistic complementarity to checkpoint inhibition. The combination increases T cell clonality parallelly improved efficacy. The data support the concept of enhancing anti-tumor immunologic memory by combining agonist and antagonist mechanisms, providing increased T cell density and clonality in the tumor. 1. Charych et al., NKTR-214, an Engineered Cytokine with Biased IL2 Receptor Binding, Increased Tumor Exposure, and Marked Efficacy in Mouse Tumor Models. Clinical Cancer Research, 22, 680-690, 2016

Legal entity responsible for the study: Nektar Therapeutics

Funding: Nektar Therapeutics


1079P

Efficacy and safety of nivolumab in elderly patients (pts) with advanced squamous non small cell lung cancer (Sq-NSCLC) participating in the expanded access program (EAP) in Italy


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Background: As a result of an increasing life expectancy, the incidence of lung cancer diagnosed in the elderly population is rising. Despite the high frequency of NSCLC in this population, elderly pts are frequently underrepresented in clinical trials since aging is associated with a significant prevalence of comorbid diseases. The purpose of this analysis is to focus on treatment with nivolumab in the elderly population (≥75 years) with advanced Sq-NSCLC from the EAP in Italy, namely in the real word setting representing a more realistic picture of clinical practice.

Methods: Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIIB/stage IV Sq-NSCLC. Nivolumab 3 mg/kg is administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events.

Results: Of 372 Italian pts with advanced Sq-NSCLC participating in the EAP in Italy, 70 (18.8%) were ≥75 years; of these, 68 pts were evaluable for response. With a median number of doses of 7 (range, 1–20) and a median follow-up of 4.7 months, the disease control rate was 42.9%, including 13 pts with a partial response and 17 with stable disease. Sixteen pts were treated beyond RECIST defined progression, with 5 of these who achieved a disease control. As of April 2016, median progression-free survival and median overall survival among all elderly pts were 3.2 and 7.6 months, respectively. Among 79 pts, 41 pts (51.9%) discontinued treatment for any reason except toxicity; 8 out of 20 discontinued due to AE (11.4%).

Conclusions: These results suggest that elderly population can benefit from nivolumab treatment with safety results consistent to what previously reported, supporting the use of nivolumab in this subpopulation.

Legal entity responsible for the study: Bristol Myers Squibb

Funding: Bristol Myers Squibb

Disclosure: F. Grossi: Advisory board of BMS during the conduct of the study. P. Bidoli: Advisory role for BMS on the Nivolumab EAP board and in other occasions. All other authors have declared no conflicts of interest.

1080P

Enabling successful T-cell therapy of solid tumors with oncolytic adenoviruses armed with TNF-α and IL-2

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Background: Adoptive T-cell based therapy can promote dramatic tumor regressions in pre-clinical tumor models and in patients with CD19(+) hematological tumors. However, in the case of human solid tumors, anti-tumor effects are limited by T-cell dysfunction.

The efficacy of everolimus relies on a modulation of adaptive anti-tumor T cell immunity

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Background: The rapalog everolimus that inhibit mTOR signaling are used as anti-proliferative drugs in metastatic renal cell carcinoma (mRCC). The influence of immune modulation mediated by everolimus on its antitumor efficacy is poorly investigated.

Methods: We performed a prospective immunomonitoring study in 23 mRCC patients treated with everolimus.

Results: Study showed that everolimus promoted high expansion of CD4+CD8 T cells (Teff). Everolimus exposure strongly enhanced the suppressive functions of patients' Tregs. Paradoxically, a concurrent activation of tumor-specific Th1 immunity also occurred during everolimus treatment. Interestingly, an early change of the Treg/antitumor Th1 balance can differently shapes the treatment efficacy. Thus, patients presenting a shift towards Treg decrease and high expansion of antitumor Th1 response had a better survival (PFS: 13.2 months vs 4.1 months P = 0.02). At the time of disease progression upon everolimus treatment, the majority of mRCC patients totally lost the anti-tumor Th1 response in favor to a marked increase of circulating Treg.

Conclusions: Altogether, our results describe for the first time a dual impact of host immune modulation mediated by everolimus on its antitumor efficacy is poorly investigated.

Legal entity responsible for the study: University of Helsinki

Funding: TILT Biotherapeutics Ltd

Disclosure: A. Hemminki: Shareholder in Targovax AS. Employee and shareholder in TILT Biotherapeutics Ltd. M. Surala, S. Parviainen: Employee of TILT Biotherapeutics Ltd. All other authors have declared no conflicts of interest.

A rational approach to dose optimisation of pembrolizumab and nivolumab using cost analysis and pharmacokinetic modelling and simulation

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Background: Pembrolizumab and nivolumab are PD-1L inhibitors approved for the treatment of advanced malignancies. Both are approved based on body size (mg/kg) dosing, which can be associated with significant wastage due to available vial sizes and acquisition cost of the drug. Dose banding is using a defined set of ranges (±10%) offers an alternative approach to body weight dosing. The aim of this work is to evaluate cost and dosing using pharmacokinetic (PK) simulation and data from 42 patients entered into the MHRA Early Access to Medicines Scheme for pembrolizumab and 24 patients enrolled in checkmate-172 trial for nivolumab.

Methods: Consecutive patients receiving pembrolizumab (n = 42) or nivolumab (n = 24) and with a median weight of 79 Kg (range 44-130Kg) and 73 Kg (range 52-103Kg) respectively were analysed. The costs were based on 12 weeks of treatment which was the time to be first assessment for both drugs. This was 4 cycles of pembrolizumab every 21 days (Q2W) and 6 cycles of nivolumab every 14 days (Q2W).

Results: 1000 random individuals were evaluated in a simulated study for pharmacokinetic and pharmacodynamic assessment. Published population PK models were used to simulate exposure and probability of trough levels achieving target level (10ng/mL) for maximum target engagement or receptor occupancy for pembrolizumab and nivolumab respectively.

Results: The costs of different strategies are illustrated in Table 1. The table also include simulated area under the curve (over the last two cycles) and mean probability of trough levels (after the first cycle of treatment) achieving 10ng/mL or receptor occupancy for the different dosing strategies.

**Table 1082P**

<table>
<thead>
<tr>
<th>Pembrolizumab</th>
<th><strong>Cost of 4 cycles (n = 42)</strong></th>
<th>Relative Drug Cost Saving (vs EXP)</th>
<th>Simulated AUC Mean mg/day</th>
<th>Mean prob of Target Engagement</th>
<th>Mean prob of Receptor Occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2mg/kg (Dose Band = 10%)</td>
<td>836,340</td>
<td>0%</td>
<td>1387 (460)</td>
<td>0.52</td>
<td>0.91</td>
</tr>
<tr>
<td>150mg Fixed dose</td>
<td>662,760</td>
<td>-19%</td>
<td>1387 (460)</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>200mg Fixed dose</td>
<td>831,690</td>
<td>-8%</td>
<td>1489 (542)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>PK derived</td>
<td>1094,520</td>
<td>-17%</td>
<td>1437 (383)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Nivolumab Q2W</td>
<td>Cost of 6 cycles (n = 24)</td>
<td>Mean mg/day</td>
<td>Mean prob of Target Engagement</td>
<td>Mean prob of Receptor Occupancy</td>
<td></td>
</tr>
<tr>
<td>3mg/kg (Dose Band = 10%)</td>
<td>406,133</td>
<td>0%</td>
<td>2088 (879)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>150mg Fixed dose</td>
<td>472,541</td>
<td>-8%</td>
<td>2036 (845)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>200mg Fixed dose</td>
<td>570,123</td>
<td>-6%</td>
<td>2280 (895)</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>PK derived</td>
<td>1865,326</td>
<td>-10%</td>
<td>2088 (820)</td>
<td>0.91</td>
<td></td>
</tr>
</tbody>
</table>

**UK cost excluding VAT, company’s submission**

Conclusions: Banded fixed dose strategies result in comparable levels of exposure and target engagement or receptor occupancy and can offer significant cost reduction. Vial size availability can contribute to the level of savings to be gained. Legal entity responsible for the study: Kayode Ogungbenro

Funding: N/A

Disclosure: R. Duncombe: Paid consultant to Bayer, Janssen, Amgen, Pfizer, MSD; Roche; Sanofi Support for travel from Novartis. No funding received for this study. P. Lorigan: Paid consultant to BMS, Merck, Amgen, Novartis, Roche, GSK and Chugai. Support for travel from BMS and Merck. No funding received for this study. All other authors have declared no conflicts of interest.

CXCL12 inhibition with NOX-A12 (alastped pegol) increases T and NK cell infiltration and synergizes with immune checkpoint blockade in tumour-stroma spheroids

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Background: Effective cancer immunotherapy requires physical contact between cytotoxic immune cells and malignant cells which is restricted by the tumour microenvironment (TME). The chemokine CXCL12 has recently been described as an important T cell exclusion factor in the TME-driven immune suppression. In this study we aimed to investigate whether CXCL12 inhibition by the clinical stage L-targeter (Spiegelmer®) NOX-A12 is able to enhance immune cell infiltration into 3D tumour-stroma spheroids.

Methods: We established 3D multicellular spheroids that mimic a solid tumour with a dissociated for analysis of infiltrated immune cells by flow cytometry. In parallel, peripheral blood mononuclear cells from healthy donors were added to the spheroids

Results: The best results were obtained when virally coded IL2 and TNFa were both used with injections were given in combination with intraperitoneal adoptive transfer of OT-1 cells. Infiltration of OT-1 T cells into the spheroids could be enhanced by the combined treatment with CXCL12 inhibition and immune checkpoint blockade.

Conclusions: CXCL12 inhibition with NOX-A12 (alastped pegol) increases T and NK cell infiltration and synergizes with immune checkpoint blockade in tumour-stroma spheroids.
with matching tumour cells, NOX-A12 also enhanced activation of T cells and synergized with PD-1 checkpoint inhibition.

Conclusions: Mechanistically, NOX-A12 appears to generate CCL12 gradients within the densely packed in vitro tumour structure and may thereby break the immune privilege of the TME in vivo. Furthermore, a lower monocyte-to-lymphocyte ratio, as found in NOX-A12 treated splenoids, has been recognized as an indicator for better prognosis in various cancer types. These data provide a rationale for the combination of NOX-A12 with checkpoint inhibitors as well as other T and NK cell-based therapies in cancer patients, such as CAR-T and CAR-NK.

Legal entity responsible for the study: Noxon Pharma AG

Funding: Noxon Pharma AG


1084P Safety of immune check-point inhibitors in patients with autoimmune conditions and advanced cancer

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Background: Immune check-point inhibitors (ICI) have revolutionised the treatment of advanced cancer. However, ICI treatment is associated with immune related adverse events (irAEs) leading to patient morbidity and mortality. Safety and efficacy of ICI is not well known in patients with auto-immune (AI) conditions as historically this group has been excluded from clinical trials. The aim of our study was to evaluate the safety and efficacy of primarily anti-PD1 therapy in patients with known AI conditions.

Methods: This was a retrospective analysis of patients with advanced cancer treated with ICI at 5 Australian hospitals.

Results: 17 patients were identified: melanoma (11), NSCLC (5) and 1 with mRCC. AI conditions: Crohn’s disease (1), Ulcerative colitis (3), rheumatoid arthritis (5 including 1 with common variable immune-deficiency), psoriasis (4) and 4 patients with other AI disease. Treatment received: Nivolumab (7 including 1 with prior Ipilimumab), Pembrolizumab (8) and Ipilimumab (2). 11 patients previously received systemic therapy for their AI condition, 2 had topical therapy and 4 had no previous therapy. Two patients had symptoms of active AI disease at time of starting ICI. Disease flared in 6/17 (35%) with G2 arthritis (2 treated with moderate dose steroids, one with anti-inflammatories), G3 colitis treated with high dose steroids, G3 dyspnoea treated with high dose steroids and G2 psoriatic rash treated with low dose steroids. Nil required steroid sparing agents. irAEs unrelated to AI disease flare: 3 patients with pneumonitis, two G2, one G3 all requiring high dose steroids and one patient with G3 colitis requiring high dose steroids. Response rates: complete (1), partial (7), stable (2) progressive disease (5), non-evaluable (2).

Conclusions: Disease flared in 35% of patients with AI conditions undergoing treatment with ICI. Most patients were successfully managed with steroids and treatment was permanently discontinued in only one patient. Although use of ICI in patients with AI conditions seems generally manageable, our data should be interpreted with caution as many patients with AI conditions had no symptoms of active disease at the start of therapy. Response to ICI is similar to historical controls.

Legal entity responsible for the study: G Gard and M Khattak

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

1085P Dendritic cell vaccination in combination with docetaxel for patients with prostate cancer – a randomized phase II study

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Background: In this study we investigate whether the addition of an autologous dendritic cell (DC) based cancer vaccine provokes an immune response in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with docetaxel based chemotherapy.

Methods: 43 patients were randomized 1:1 to receive up to 10 cycles of docetaxel alone, 75 mg/m2 on strived cycles 1-4, or in combination with an autologous DC based vaccine CD14+ monocytes were initially isolated from patients randomized to combination therapy according to a leukapheresis procedure. Harvested cells were incubated with GM-CSF and IL-4 and the resulting immature DCs were further matured using IL-1β, TNFα, IL-6 and PGE2 mRNA encoding prostate specific antigen, prostatic acid phosphatase, survivin and tERT was transfected into mature DCs using electroporation. Vaccines were administered intradermally at day 8 and 15 through treatment cycles 1-4 and at day 8 only through treatment cycles 5-10. Delayed type hypersensitivity (DTH) tests were applied. Immune cell composition and antigen specific responses in blood samples were analyzed using flow cytometry and ELISPOT. Prostate cancer clinical trials working group 2 guidelines were followed. Toxicity was graded according to CTC AE version 4.0. Progression free survival (PFS) and disease specific survival (DSS) was calculated using the Kaplan-Meier method.

Results: Baseline mrCPRC prognostic factors were equally distributed in the two treatment groups. Median number of treatment cycles was 7. Rates of grade 2-4 PSA-responses were 63% vs 38% (p = 0.11) in the docetaxel alone (n = 19) and combinational therapy group (n = 21), respectively. Median PFS and DSS was 5.5 vs 5.7 months (p = 0.62, log-rank) and 24.7 vs 25.1 months (p = 0.70, log-rank). Vaccine induced toxicity was limited to mild local skin reactions and pain. Analysis of chemokine induction, DTH and immune monitoring is currently ongoing and will be presented.

Conclusions: The addition of an autologous DC based cancer vaccine was safe in this study. Survival endpoints were similar in both groups of patients investigated.

Clinical trial identification: ClinicalTrials.gov NCT01446731

Legal entity responsible for the study: N/A

Funding: Center for Cancer Immune Therapy and Department of oncology, Herlev University Hospital

Disclosure: All authors have declared no conflicts of interest.

1086P Safety of the natural killer (NK) cell-targeted anti-KIR antibody, flirlubam (liri), in combination with nivolumab (nivo) or ipilimumab (ipii) in two phase 1 studies in advanced refractory solid tumors

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Background: NK cells play a critical role in immune surveillance and control of tumor growth. Killer-cell immunoglobulin-like receptors (KIR) are important in regulating NK cell function and anti-tumor immune response, particularly in combination with other immune-related adverse events (irAEs) leading to patient morbidity and mortality. Safety and efficacy of ICI is not well known in patients with autoimmune (AI) conditions as historically this group has been excluded from clinical trials. The aim of our study was to evaluate the safety and efficacy of primarily anti-PD1 therapy in patients with known AI conditions.

Methods: This was a retrospective analysis of patients with advanced cancer treated with ICI at 5 Australian hospitals.

Results: 17 patients were identified: melanoma (11), NSCLC (5) and 1 with mRCC. AI conditions: Crohn’s disease (1), Ulcerative colitis (3), rheumatoid arthritis (5 including 1 with common variable immune-deficiency), psoriasis (4) and 4 patients with other AI disease. Treatment received: Nivolumab (7 including 1 with prior Ipilimumab), Pembrolizumab (8) and Ipilimumab (2). 11 patients previously received systemic therapy for their AI condition, 2 had topical therapy and 4 had no previous therapy. Two patients had symptoms of active AI disease at time of starting ICI. Disease flared in 6/17 (35%) with G2 arthritis (2 treated with moderate dose steroids, one with anti-inflammatories), G3 colitis treated with high dose steroids, G3 dyspnoea treated with high dose steroids and G2 psoriatic rash treated with low dose steroids. Nil required steroid sparing agents. irAEs unrelated to AI disease flare: 3 patients with pneumonitis, two G2, one G3 all requiring high dose steroids and one patient with G3 colitis requiring high dose steroids. Response rates: complete (1), partial (7), stable (2) progressive disease (5), non-evaluable (2).

Conclusions: Disease flared in 35% of patients with AI conditions undergoing treatment with ICI. Most patients were successfully managed with steroids and treatment was permanently discontinued in only one patient. Although use of ICI in patients with AI conditions seems generally manageable, our data should be interpreted with caution as many patients with AI conditions had no symptoms of active disease at the start of therapy. Response to ICI is similar to historical controls.

Legal entity responsible for the study: G Gard and M Khattak

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
A mechanism of action study of intra-tumoral or intravenous dosing of enadenotucirev, an oncolytic adenovirus in patients with colon, lung, bladder and renal carcinoma undergoing resection of primary tumor

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Background: Demonstrating intra-venous (IV) delivery in patients is key for the development of enadenotucirev (EnAd), a tumor selective chimeric Ad11/Ad3 group B adenovirus. Initial results from colon cancer (CC) patients receiving intra-tumoral (IT) or IV administration have been reported [ESMO 2015 Abstract 1086P]. Here we report the full study results, including an expansion to include lung (NSCLC), bladder and renal (RCC) cancer patients. The primary study objective was to describe the pattern of EnAd delivery within tumors.

Methods: Patients with histologically confirmed cancer scheduled for surgical removal of primary tumor received either 1x10^10 viral particles (VP) IV over 5 min on D 1, 3 and 5, or 10^11 VP/ml IT with a variable volume injected based on the tumor surface area on D 1. Immunohistochemistry (IHC) staining was performed on formalin fixed (FFPE) sections for EnAd specific virus and IHC staining and qPCR confirm that IV dosing can deliver EnAd selectively to all 4 tumor types and is as reliable as IT in CC. Evidence of enhanced immune responses in tumors included high levels of CD8+ cells within tumor nests and peritumoral stroma. CD4+ cells were largely restricted to stroma. Nanotargeting highlighted potential treatment-responsive genes for further evaluation.

Conclusion: Delivery of EnAd to tumor cells following IV dosing has been confirmed by IHC and qPCR studies. In surgically resected tumor samples from patients with CC, NSCLC, RCC and bladder cancer. Delivery appears to be associated with inflammatory changes within the first weeks after administration.

Clinical trial identification: EudraCT 2012-001067-79

Legal entity responsible for the study: PsiOxus Therapeutics Limited

Funding: PsiOxus Therapeutics Limited

Disclosure: B. Champion, S. Alvis, K. Fisher, H. McElwaine-Johnn, C. Ellis Stock options in PsiOxus. J. Beadle: Chief Executive Officer, serves as a board member and holds stock options in PsiOxus. All other authors have declared no conflicts of interest.

1088P Comprehensive assessment of the feasibility of adoptive cell therapy in colorectal carcinoma

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Background: Adoptive cell therapy (ACT) can induce objective clinical responses in solid tumors. However, its potential in colorectal cancer (CRC) remains poorly explored. To this end, several questions need to be addressed: Can tumor-infiltrating lymphocytes (TIL) be isolated from CRC, including cryopreserved samples? Can the contamination by the gut microbiota be circumvented? Are CRC TIL similar to those exploited in melanoma trials?

Methods: Cryopreserved samples (n = 10) were obtained from primary colon adenocarcinoma tumors (n = 5) or liver metastasis (n = 5). Disected fragments (n= 10 - 32) were plated and stimulated with IL-2 (6000 IU/ml) for 21-28 days (pre-REP). A rapid expansion protocol (REP) consisting of a polyclonal stimulation with PHA was performed in cases where the pre-REP yield was low (< 5x10^6 TIL). Microbiological testing (BD BACTEC™) was performed at Day 0 (D0) and was repeated at D14 of the pre-REP after culturing in antibiotic-containing media. Polychromatic flow cytometry analyses were performed at harvest.

Results: Sufficient TIL were successfully obtained from all patients tested. The yield of TIL at harvest was broad, not linked to fragments numbers and ranged from 10^4 to 10^7 cells (198 ± 90.9 x10^6, mean ± SEM). Only 4/10 patients required a secondary REP to reach >50 x10^6 TIL. Among the primary tumors, the highest potential for TIL isolation was observed for the right-side colon tumors, as opposed to the left-side (478 ± 329 x10^6 vs 5.3 ± 5.8 x10^6 cells), while no significant difference was observed between primary and metastatic samples. Bacterial contamination was detected at D0 in all primary tumors (and none in metastatic samples; p = 0.02, g2), but microbiological tests turned negative at D14. Flow cytometry analyses showed that T cells represented 78 ± 6% of the pre-REP TIL with CD3/CD4 ratios ranging from 0.3 to 1.80 (median 1.62). CD8+ T cells were 74 ± 9.4% effector memory (CCR7+CD45RA-).
Background: Non small cell lung cancer (NSCLC) comprises the majority of primary lung cancers and it is usually fatal in its advanced stages. The objective of this analysis is to assess the potential clinical and biological predictive markers of survival in pretreated advanced NSCLC patients treated with the three PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab).

Methods: MEDLINE and EMBASE databases have been searched. Randomized clinical trials comparing the three PD-1/PD-L1 inhibitors versus other treatments for the management of Pretreated advanced NSCLC were evaluated.

Results: Four randomized trials with 2163 included. Two studies evaluated nivolumab (nivolumab/docetaxel, one study evaluated pembrolizumab versus docetaxel and one study evaluated atezolizumab versus docetaxel). Comparing EGFR mutant to wild type disease, patients with EGFR wild type disease derive greater benefit from PD-1/PD-L1 inhibitors. The pooled HR for death for patients with mutant disease was 1.05 [95% CI: 0.89, 1.20; P = 0.81], while pooled HR for death for patients with wild type disease was 0.66 [95% CI: 0.57, 0.77; P < 0.00001].

Conclusion: Further controlled studies are required to properly confirm the predictive value of PD-L1 and EGFR statuses in this setting as well as evaluate more clearly the predictive roles of smoking, KRAS status and CNS metastasis. Legal entity responsible for the study: N/A Funding: AIN Shams University Disclosure: All authors have declared no conflicts of interest.
Methods: Medical records of melanoma patients treated with ICPI at the Royal Marsden Hospital from 2010–2015 were reviewed. The grade, duration of CS and infliximab (INF) use was recorded for each D/C episode. Patients who had flexible sigmoidoscopy (FS) were labeled as having macroscopic +/- microscopic (macro), microscopic changes alone or no changes (normal). CS strategies are presented.

Results: 414 ICPI treatment episodes were undertaken in 353 patients. The rate of all-grade D/C was 23% (96/414); 27% (77/282) with ipilimumab, 8% (8/101) with anti-CTLA-4 agents and 38% (8/21) with combination ipilimumab + nivolumab. Median age 61 years, 54% were male.

Conclusions: Appearance at FS may predict for duration of CS use and considered for PJP prophylaxis. CS sparing strategies should be prospectively evaluated.

Legal entity responsible for the study: James Larkey

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
having difficulties recovering from lymphodepleting chemotherapy before T cell therapy. The treatment consists of high-dose chemotherapy (60 mg/kg cyclophosphamide for 2 days and 25 mg/m² fludarabine for 5 days) followed by T cell administration and subsequent high-dose decrescendo interleukin-2 for up to 5 days. Patients are evaluated for up to 5 years or until progression.

**Results:** Five patients are presently included and 3 have received T cell therapy. One had a partial metabolic response, stable disease (SD) with nearly 20% tumor regression and > 50% reduction of CA-125 at 6 weeks, but progressive disease (PD) at 12 weeks. The second had SD at 6 weeks with a small decrease in CA-125, but PD at 12 weeks. The third had SD at 6 weeks with a 25% drop in CA-125 and awaits 2nd evaluation. Only expected and manageable toxicities have been observed and all patients recovered without the need of stem cell support. Immune analyses are pending.

**Conclusions:** So far, T cell therapy for patients with advanced OC seems to be manageable and tolerable.

**Clinical trial identification:** Clinicaltrials.gov ID: NCT02482090

**Legal entity responsible for the study:** Center for Cancer Immune Therapy

**Funding:** Center for Cancer Immune Therapy University of Copenhagen Kræftens Bekæmpelse OvaCare

**Disclosure:** All authors have declared no conflicts of interest.

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**Expression pattern of immune checkpoint-associated molecules in radical nephrectomy specimens as a prognostic predictor in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors**

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**Background:** It has not been established whether activation of immune checkpoint pathways is correlated with the clinical course of systemic therapies for metastatic renal cell carcinoma (mRCC), particularly tyrosine kinase inhibitors (TKIs). The objective of this study was to analyze the expression pattern of immune checkpoint-associated molecules in tumor tissues to determine the prognostic significance of these molecules in mRCC patients treated with TKIs.

**Methods:** Radical nephrectomy specimens were obtained from 62 patients treated with TKIs as first-line systemic therapy for mRCC. The proportions of programmed death-1 (PD-1)-positive tumor infiltrating lymphocytes (TILs) as well as those of tumor cells positive for PD-1-ligand 1 (PD-L1) and PD-L2 were analyzed by immunohistochemical staining.

**Results:** Twelve patients (19.3%) were revealed to be positive for PD-1-positive TILs, while positive expression of PD-L1 and PD-L2 were detected in 12 (19.3%) and 10 (16.1%) patients, respectively. Patients with positive PD-L1 expression had significantly unfavorable progression-free survival (PFS) compared with those without positive PD-L1 expression, despite the remaining two molecules having no significant impact on PFS. Additionally, overall survival (OS) in patients positive for PD-L1, PD-L1 or PD-L2 expression was significantly poorer than that in those without expression of each immune checkpoint-associated molecule. Multivariate analyses of several parameters identified the following independent prognostic predictors after the introduction of TKIs: PD-L1 expression status for PFS, and lymph node metastasis, Memorial Sloan-Kettering Cancer Center classification and expression statuses of PD-1-positive TILs and PD-L1 for OS.

**Conclusions:** Positive expression of immune checkpoint-associated molecules in tumor tissues, particularly that of PD-L1, could be useful prognostic indicator in mRCC patients receiving TKIs as first-line systemic therapy.

**Legal entity responsible for the study:** N/A

**Funding:** Kobe University

**Disclosure:** All authors have declared no conflicts of interest.

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**Assessment of nivolumab (Nivo) benefit-risk profile from a 240-mg flat dose versus a 3-mg/kg dosing regimen in patients (Pts) with solid tumors**

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**Background:** Nivo 3 mg/kg every 2 weeks (Q2W) has shown overall survival (OS) benefit over the standard of care in multiple advanced cancers and is currently approved for treatment of renal cell carcinoma (RCC), melanoma (MEL), and squamous and non-squamous non-small cell lung cancer (SQ/NOS NSCLC) in the US, EU, and other countries. Nivo, a programmed death-1-blocking antibody, displays flat exposure-response (E-R) relationships. Relative to body weight (BW)-based dosing, a flat dose is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. This integrated analysis evaluated the exposure, efficacy, and safety of a 240-mg flat dose relative to 3-mg/kg dosing in the approved indications.

**Methods:** A flat dose of 240 mg was selected based on equivalence to the approved 3-mg/kg dose at the median BW of ~80 kg in pts with solid tumors. Demographic data from pts with RCC (n = 603), MEL (n = 826), or SQ/NOS NSCLC (n = 648) across 9 CheckMate studies were included in the pooled dataset. Exposures produced by doses of 3 mg/kg or 240 mg Q2W were simulated based on established quantitative pharmacokinetic models and further used to predict efficacy and safety from E-R models in each tumor type. A safety review of clinical data in pts with solid tumors who received nivo 3 or 10 mg/kg was conducted to evaluate the association between BW or exposure measures and incidence of adverse events (AEs).

**Results:** The geometric mean of summary measures of nivo exposure predicted from the 240-mg flat dose Q2W was ≤5% different than corresponding exposures produced by 3-mg/kg Q2W dosing. The predicted OS benefit and risk of AEs leading to discontinuation or death were similar across tumor types for both dosing regimens. Subgroup safety analyses did not demonstrate a clinically meaningful relationship between nivo exposure or BW and frequency or severity of AEs.

**Conclusions:** Based on model-predicted nivo pharmacokinetics, efficacy, and safety, clinical safety review, and an understanding of nivo E-R relationships, no clinically meaningful difference in the benefit-risk profile of nivo is expected with 240-mg Q2W vs 3-mg/kg Q2W dosing in RCC, MEL, or NSCLC.

**Legal entity responsible for the study:** Sponsored by Bristol-Myers Squibb

**Funding:** Sponsored by Bristol-Myers Squibb

**Disclosure:** S. Suryawanshi, M. Hruska, B. McHenry, I.M. Waxman, A. Roy. Employee of and stock ownership in Bristol-Myers Squibb. X. Wang, J. Shen, A. Achanta, A. Bello: Employee of Bristol-Myers Squibb. S. Agrawal: Employee of and stock ownership in Bristol-Myers Squibb. Stock Ownership in Eli Lilly and Celldex. All other authors have declared no conflicts of interest.
An open-label, multicenter, phase I study of ramucirumab (R) plus durvalumab (D) in patients (pts) with locally advanced and unresectable or metastatic gastric or gastroesophageal junction (G/E/J) adenocarcinoma, non-small cell lung cancer (NSCLC), or hepatocellular carcinoma (HCC)

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Background: Hallmarks of tumor growth include angiogenesis and immunosuppression, and combining R (anti-vascular endothelial growth factor receptor 2 antibody) with D (anti-programmed death ligand-1 antibody) to target both processes demonstrates synergy in preclinical models. This global phase I trial (NCT02572687) will assess safety, toxicities, pharmacokinetics, immunogenicity, and preliminary efficacy of the combination in pts with locally advanced and unresectable or metastatic G/E/J adenocarcinoma, NSCLC, or HCC.

Trial design: Key inclusion criteria include pts who have progressed on therapies, can provide a tumor biopsy sample, and have an ECOG PS of 0-1. Two combination dose/schedules will be evaluated in the Phase Ia dose limiting toxicity (DLT) observation phase, following 0 + 3 dose de-escalation with a starting dose of R (10 mg/kg intravenous [IV]) and D (1125mg IV) QW for NSCLC and R (8 mg/kg IV) and D (750 mg IV) QW for G/E/J and HCC (1 treatment cycle [21 days for the NSCLC cohort and 28 days for the Gastric-G/E/J and HCC cohorts]). Phase Ia will include 18-34 pts. After the Phase Ia/DLT evaluation, each cohort will be expanded to approximately 20 pts who will receive study treatment until confirmed disease progression or unacceptable toxicity (Phase Ib). A final analysis will be performed 12 months after the last patient’s first dose of study treatment. The primary objective is the assessment of the safety and tolerability of the combination of R + D, and the secondary objectives are pharmacokinetics (Phase Ia/IB) and preliminary efficacy and immunogenicity (Phase IB). Interim analyses will occur on all pts within a cohort have completed (or discontinued from) approximately 24 weeks of treatment.

Clinical trial identification: NCT02572687
Legal entity responsible for the study: Eli Lilly and Company
Funding: Eli Lilly and Company
Disclosure: Y.-J. Bang: Research fundings (through the institution) from Lilly, and consulting roles of Lilly; L.W. Goi: Advisory role for Celgene; research funding from Astellas Pharma, Pfizer, Onyx, Sun Pharma, Lilly, and Bristol-Myers Squibb. H. Wasserstrom, J. yang. G. M: Employee of Eli Lilly and Company and holds equity in the company. M. Reck: Advisory role for Boche, Lilly, Bristol-Myers Squibb, AstraZeneca, Pfizer, Boehringer-Ingelheim, and Celgene. All other authors have declared no conflicts of interest.

Phase II multi-centre, non randomized, open label study of nivolumab in combination with ipilimumab as first line in adults patients with metastatic uveal melanoma. GEM 14-02

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Background: Uveal melanoma (UM) is the most common primary intraocular malignancy in adults (6 cases per million). Up to 35% of patients develop metastatic disease affecting primarily the liver (95%). After systemic dissemination the prognosis is poor, estimated median Overall Survival (mOS) of 6 months (m) without treatment. Efficacy of conventional chemotherapy is limited, with overall response rate round 5% and mOS 8-10 m. Trials evaluating new targeted therapies (e.g. MEK inhibitors) have failed to achieve positive results. As a result mOS of metastatic UM patients has not improved in the last 25 years. UM cells express PD-1,L1, and have others characteristics that suggest they could respond to immune-checkpoint blocking antibodies. Indeed our group recently reported a study of Ipilimumab 10mg/kg with promising results, mOS 10 months. 48% alive at 1y: The above mentioned lead us to design this trial with the hypothesis that combination of Nivolumab and Ipilimumab will improve OS on these patients.

Trial design: This is a phase II, multi-center, non randomized, open label study of nivolumab combined with ipilimumab in subjects with previously untreated metastatic uveal melanoma. Patients must have histologically confirmed uveal melanoma, with progressive metastatic disease at baseline, >18y old and adequate organ function. Prior systemic treatment and autoimmune or infectious diseases are the main exclusion criteria. Dosing schedule is described in Table 1. Patients will be treated until progression, unacceptable toxicity or patient withdrawal. Selected cases will be treated beyond progression specified per protocol. Objectives: Primary Endpoint is 1 year OS. Safety, PFS according to RECIST 1.1 criteria and correlation between biomarkers and clinical results will be evaluated. Statistics: Predicted sample size is 48pts. H1:1yOS= 27% (pooled external data). H2:1yOS= 50%.

Legal entity responsible for the study: Grupo Español Multidisciplinar de Melanoma
Funding: Bristol-Myers-Squibb
Disclosure: All authors have declared no conflicts of interest.

A phase 1b/2 dose escalation and cohort expansion study of the safety, tolerability and efficacy of a transforming growth factor receptor I (TGF-$\beta$) receptor I kinase inhibitor (galunisertib) in combination with anti-PD-1 (nivolumab) in advanced refractory solid tumours

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Background: TGF-$\beta$-signaling plays an important role in tumorigenesis and contributes to the hallmarks of cancer, including tumor proliferation, invasion and metastasis, inflammation, angiogenesis, and escape of immune surveillance. Galunisertib (LY2157299 monohydrate) is an oral small molecular weight inhibitor of the TGF-$\beta$ receptor I kinase that specifically down-regulates the phosphorylation of SMAD2, abrogating activation of the canonical pathway. Programmed Cell Death 1 (PD-1) is expressed on activated $T$ cells and can act to dampen the immune response. Tumor cells overexpress PD-1 ligand (PD-L1) and inhibit the local immune response. Nivolumab blocks the binding of PD-L1 to its PD-1 receptor, allowing the activated $T$ cells to identify and attack cancer cells. Thus, blockade of both TGF-$\beta$ and PD-L1 could be expected to reverse the immune escape and to potentially provide immune restoration to improve immune response and induce tumor regression.

This study (NCT02423343) is a phase 1b/2-open label study that will be conducted in 2 parts. The phase 1b is an open-label, dose-escalation assessment of the safety and tolerability of galunisertib administered in escalating doses over 4 cohorts ending with 150 mg BID in combination with nivolumab 3 mg/kg IV every 2 weeks in patients with advanced refractory solid tumors. The phase 2 will be disease restricted and includes 3 expansion cohorts of patients with non-small cell lung cancer (n = 25), hepatocellular carcinoma (n = 25), or glioblastoma (n = 25). Patients in the 3 cohorts will be assigned to treatment concurrently, and enrollment will be complete when all cohorts have reached the prespecified enrollment target. Enrollment of patients in phase 1b began on 09 October 2015, as of 27April2016, seven patients entered the study; one withdrew for a non-DLT reason, and one patient remains on treatment every 2 weeks.

Clinical trial identification: NCT02423343
Legal entity responsible for the study: Eli Lilly and Company
Funding: Eli Lilly and Company
Disclosure: S.C. Guba, D. DeSaia, V.A.M. Andre. Author is an employee of Eli Lilly and Company and holds company stock. All other authors have declared no conflicts of interest.
MEDIOLA: A phase I/II, open-label trial of olaparib in combination with durvalumab (MED14736) in patients (pts) with advanced solid tumours

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Background: Olaparib (Lynparza) is a potent, oral PARP inhibitor that induces synthetic lethality in tumours deficient in homologous recombination repair. Durvalumab is a selective, high-affinity, engineered, human IgG1 mAb that blocks the adenosine A2a receptor. MEDIOLA (NCT02484404) is using this combination dose to assess olaparib and durvalumab, which may have complementary mechanisms of action, in pts selected using criteria that predict sensitivity to olaparib.

Trial design: MEDIOLA has two phases: cohorts: pts with platinum-sensitive recurrent ovarian cancer (OC) who have received ≥2 lines of platinum-based therapy and have a known/suspected deleterious germline BRCA1/2 mutation (gBRCAm), pts with unselectable, advanced, gBRCAm, HER2-negative breast cancer (BC) who have received anthracycline/taxane therapy, pts with small-cell lung cancer (SCLC) that has relapsed >12 weeks (wks) after platinum-based therapy; and pts with advanced ATM-negative gastric cancer (GC) that has progressed after first-line chemotherapy. Pts will receive olaparib monotherapy (300 mg bd, tabled) for 4 wks, then olaparib (300 mg bid) plus durvalumab (1500 mg IV q4w) until disease progression. Disease will be assessed by CT/MRI at baseline, after olaparib monotherapy and every 8 wks during the combination phase. Primary objectives are disease control rate (DCR) at 12 wks (includes pts with complete/partial response or stable disease) by modified RECIST 1.1 (using a post-progression scan), safety and tolerability. Secondary endpoints include pharmacokinetics, DCR at 28 wks, objective response rate, progression-free survival and overall survival. Cohorts will be considered as individual Bayesian predictive probability designs. Initially, 10 pts/cohort will be enrolled across 16 centres worldwide, with expansion to n = 37 (GC) after interim assessment. Enrolment began in Q1 2016.

Clinical trial identification: NCT02734004
Legal entity responsible for the study: AstraZeneca
Funding: AstraZeneca

Disclosure: S. Domchek: The University of Pennsylvania has received research funding from AbbVie, and Clovis. Dr. Domchek has received an honorarium from EMD Serono. Y-J. Bang: Research funds from AstraZeneca (through institution), and from AbbVie, and Clovis. Dr. Domchek has received an honorarium from EMD Serono. S. Domchek: The University of Pennsylvania has received research funding from AstraZeneca.

Intravenous cossacivirus A21 in combination with pembrolizumab in advanced cancer patients: phase Ib KEYNOTE 200 study

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Background: CV A21 is a novel, bio-selected ICAM-1-targeted immunotherapeutic Cossacivirus A21 (CV A21). Infection of the tumour micro-environment by CV A21 can increase levels of immune-checkpoint molecules, immune-cell infiltration and enhancement of systemic antitumour immune response. Pembrolizumab is a human programmed death receptor 1 (PD-1) blocking antibody that has induced responses in a number of tumour types via reversal of tumour-induced T-cell suppression. Preclinical studies in immune-competent mouse models of NSCLC and melanoma suggest synergistic combinations of IV CV A21 + anti-PD-1 mAbs mediate greater antitumour activity compared to single agent use. As such, we propose that the combination of CV A21 + pembrolizumab may translate to similar benefits in the clinic. The KEYNOTE 200 Phase Ib study (NCT02453665) assesses tolerance and efficacy of IV-delivered CV A21 ± pembrolizumab in advanced cancer pts.

Trial design: Primary objectives are to assess dose-limiting toxicities (DLT) of CV A21 ± pembrolizumab. Secondary objectives include ORR by irRECIST criteria, PFS, and OS. Treatment: Part A: Pts are infused with CV A21 in Cohort 1 (n = 3), at a dose of 1 x 109 TCID50, in Cohort 2 (n = 3) at a dose of 3 x 109 TCID50, and in Cohort 3 (n = 12-18) at a dose of 1 x 109 TCID50 on study days 1,5,22 and Q3W for 6 additional infusions. Part A enrollment is almost complete. Part B: Pts are infused with CV A21 ± pembrolizumab. In Cohort 1 (n = 5), CV A21 is administered at a dose of 1 x 109 TCID50 in Cohort 2 (n = 3) at a dose of 3 x 109 TCID50, and in Cohort 3 (n = 8-10) at a dose of 1 x 109 TCID50 on study days 1,5,22,29 and Q3W for 6 additional infusions. All subjects receive pembrolizumab at 200 mg IV Q3W from Day 8 for up to 2 years. Treatment with IV CV A21 ± pembrolizumab will continue until confirmed CR or PD (whichever comes first) per irRECIST or DLT. Key eligibility: Pts with advanced disease, lesion(s) accessible for core biopsy. ECOG PS 0-1, no active cerebral metastases, no autoimmunity/immunosuppression.

Clinical trial identification: NCT02453665
Legal entity responsible for the study: Viralytics Limited
Funding: Viralytics Limited


Phase 1/1b multicenter trial of the adenosine A2a receptor antagonist (A2aR) CPI-444 as single agent and in combination with atezolizumab (ATZ) in patients(Pts) with advanced cancers

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Background: Adenosine is an extracellular signaling molecule that increases in response to acute tissue injury/inflammation to restore tissue homeostasis. Elevated levels of adenosine are produced in the tumor microenvironment and signaling through A2A receptors on immune cells leads to immunosuppression, promoting tumor growth. CPI-444 is an oral A2A receptor antagonist that has been evaluated in phase 1 and 2 clinical trials outside the oncology setting. CPI-444 binds to A2aR with a Kᵢ of 3.5 nM and > 50 fold selectivity over other adenosine receptor subtypes. Preclinical studies with various tumor models demonstrate efficacy of CPI-444 as a single agent (SA) and in combination with anti-PD1/PDL1 immunotherapies.

Trial design: We have initiated a phase 1/1b multicenter, open label trial to evaluate CPI-444 as a SA and in combination with ATZ (anti-PDL1), in pts with advanced cancers. The objectives are 1)Evaluate the safety and tolerability of multiple dose rates of CPI-444 2) Identify a recommended dose and schedule for further study and 3) evaluate efficacy. Eligibility criteria: 1Histology: non-small cell lung cancer, melanoma, renal cell cancer, triple-negative breast cancer, bladder cancer, head and neck cancer and MSI colorectal cancer and 2) 1 but not more than 5 prior therapies. This phase 1/1b adaptive design is composed of 2 steps with multiple expansion cohorts within Step 2 based on a 3-stage expansion design. Step 1 is a dose selection step with 4 cohorts (3 SA cohorts with CPI-444 at various dosing schedules and 1 cohort combined with ATZ). After Step 1, the optimal dose SA cohort of CPI-444 determined by safety and other biomarkers and the optimal dose from the combination cohort will proceed to Step 2. Step 2 has 10 multiple expansion cohorts: 5 cohorts (stratified by disease) will receive CPI-444 as a SA and 5 cohorts will receive the combination. The total sample size is up to 534 pts. This trial is accruing in N America and will expand to Australia and Europe.

Clinical trial identification: NCT02655822
Release date: January 08, 2016
Legal entity responsible for the study: Corvus Pharmaceuticals
Funding: Corvus Pharmaceuticals

melanoma and other skin tumours

Table: 1106C

<table>
<thead>
<tr>
<th></th>
<th>IPI 10 mg/kg</th>
<th>IPI 3 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>15.7 (11.6–17.8)</td>
<td>11.5 (9.9–13.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.84 (0.70–0.99)</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>1-Year OS rate (95% CI)</td>
<td>54.3 (49.0–59.3)</td>
<td>47.6 (42.4–52.7)</td>
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<tr>
<td>2-Year OS rate (95% CI)</td>
<td>38.5 (33.4–43.5)</td>
<td>31.0 (26.2–35.6)</td>
</tr>
<tr>
<td>3-Year OS rate (95% CI)</td>
<td>31.2 (26.4–36.0)</td>
<td>23.2 (18.9–27.7)</td>
</tr>
</tbody>
</table>

Conclusions: In the first phase 3 trial to directly compare IPI 10 mg/kg vs 3 mg/kg in MEL pts who had not received prior BRAF or immune checkpoint inhibitors, IPI 10 mg/kg demonstrated improved OS vs IPI 3 mg/kg, and higher incidence of treatment-related AEs, AEs leading to discontinuation, and immune-mediated adverse reactions.

Clinical trial identification: NCT01515189

Legal entity responsible for the study: Bristol-Myers Squibb

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**Genomic features of complete responders (CR) versus fast progressors (PD) in patients treated with BRAFV600-mutated metastatic melanoma treated with cobimetinib + vemurafenib or vemurafenib alone**

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**Background:** Cobimetinib + vemurafenib and vemurafenib alone have achieved improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) in patients with BRAFV600-mutated metastatic melanoma. However, not all patients with BRAFV600-mutated metastatic melanoma benefit equally from these regimens. Several factors, including BRAF and MEK inhibitor resistance, have been previously associated with poor outcomes in BRAFV600-mutated metastatic melanoma. We hypothesized that the genomic landscape of patients with BRAFV600-mutated metastatic melanoma who achieve a complete response (CR) to cobimetinib + vemurafenib is different from those who progress early.

**Methods:** Genomic analysis was performed on patients with BRAFV600-mutated metastatic melanoma who achieved a CR to cobimetinib + vemurafenib and to vemurafenib alone. Genomic analysis was performed using whole-exome sequencing (WES) and RNA sequencing (RNA-Seq). Differences between CR and PD were tested by ANOVA. Gene signatures represent the mean Z-score of all components. Associations of gene expression with PFS or OS were assessed by Cox proportional hazards modeling.

**Results:** Genomic analysis showed higher rates of MITF amplification (20% vs 4%) and TP53 mutation (19% vs 5%) in PD than CR, whereas NRF1 deletion and deleterious mutations were more common in CR than PD (12% vs 3%). Mutational load was similar in CR and PD. Tumors from 32 CR and 49 PD were evaluated by RNA-Seq. Initial analysis identified 415 genes differentially expressed between groups that were also associated with PFS or OS. Innate anti-PD1 resistance signatures (IPRES, Hugo et al. Cell 2016:165:35-44) were not significantly different between PD versus CR, but gene signatures of CD8 T effector cells, cytokine T-cell effector presence, and overall proliferation were significantly enriched in CR tumors. Interestingly, 19 keratin genes and 7 kallikrein genes were expressed at significantly higher levels in PD tumors, reminiscent of the “keratin subtype” proposed by The Cancer Genome Atlas project.

**Conclusions:** These exploratory analyses revealed genomic differences between melanomas from CR vs PD treated with cobimetinib combined with vemurafenib or vemurafenib alone. Melanomas from CR possessed higher pre-existing tumor immunity features, while melanomas from PD may be overrepresented by the “keratin” molecular subtype.

**Legal entity responsible for the study:** F. Hoffmann-La Roche, Ltd.

**Funding:** This study was funded by F. Hoffmann-La Roche, Ltd.

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**Disclosure:** No relevant disclosures.
arm 1 until no injectable tumors, disease progression, or intolerance. I started with the T + I arm (attributed to I per investigator).

Results: 173 pts were randomized: 88 T + I, 85 I. Characteristics for all pts were similar: 54% stage IIIb-IVM1a, 45% IVM1b/c. Median follow up time for 82 pts was 62.1 w (range 0.14-113.9). ORR was confirmed 35.7% (T + I) and 17.5% (I), unconfirmed ORR was 50% (T + I) and 27.5% (I; table). Of 165 pts in the safety set (85 T + I, 80 I), 54% stage IIIB-IVM1a, 45% IVM1b/c. Median follow up time for 82 pts was 5.6 mo (range 1.5-113.9). All grade (G) AEs that occurred in > 20% pts and reported as related to A and/or C and/or V were nausea, fatigue, flu-like symptoms, photosensitivity, maculopapular rash, elevated ALT/AST, mucosal inflammation and arthralgia. 6 pts had C- and/or V-related G3-4 AEs during run-in period, and 5 pts had A- and/or C- and/or V-related G3-4 AEs during the triple combination period; all were manageable and reversible. There were no unexpected AEs or G5 AEs. No A-related SAEs occurred. 1 pt discontinued all study treatment due to elevated ALT/AST. 13/14 pts (93%) showed responses (RECIST v1.1), including 1 CR and 12 PRs. 1 pt had PR without a 10% reduction in target lesions. Responses were confirmed, and median DOR and PFS were not estimable due to limited follow-up at the time of data cut (Feb 15, 2016). 11/13 pts is continue in response. Updated data with functional biomarkers of T-cell activation will be presented.

Conclusions: A + C + V combination therapy results in a manageable safety profile and promising anti-tumor activity in pts with BRAFV600-mutant metastatic melanoma. These preliminary data show that anti-PD1 therapy can be successfully combined with MEK and BRAF inhibitors and warrant further exploration. NCT01656462

Clinical trial identification: NCT01656462

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd

Funding: F. Hoffmann-La Roche Ltd

Disclosure: O. Hamid. Consultant, speaker and receives funding from AstraZeneca Bristol-Myers Squibb Celldex Genentech/Roche Immunocore Incyte Merck Merck Serono MedImmune Novartis Pfizer R. Gonzalez Grant recipients received from Roche Genentech, BMS, Merck, AstraZeneca. J.R. Infante. I have no personal financial conflicts of interest but my institution receives research funding and consulting from Genentech. F.S. Hodis. Non-paid advisor to Genentech, BMS, Merck. Member of the AstraZeneca advisory board; compensated advisor to Novartis, received clinical trials support from Genentech, BMS, Merck and Novartis. J. Wallin, G. Mwawasi, E. Cha, N. Richie, M. Ballinger. Employee of Genentech, Inc. R. Sullivan. Grants from Merck, personal fees from Novartis, outside the submitted work. All other authors have declared no conflicts of interest.
PD-L1 expression as a biomarker for nivolumab (NIVO) plus ipilimumab (IPI) and NIVO alone in advanced melanoma (ME1): A pooled analysis


Background: NIVO + IPI and NIVO showed superior clinical activity vs IPI in a phase 3 trial of MEL patients (pts), irrespective of PD-L1 tumor expression. Among pts with high PD-L1 expression ≥5%, mPFS of NIVO + IPI was not reached (NR) and 56.5% vs 18.2% (ORR) were observed, respectively. As OS data have not yet matured, caution is advised when applying these results to assess the relative benefit of NIVO + IPI vs NIVO. Clinical trial identification: NA

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: G.V. Long: Served as a consultant for GSK, Roche, Novartis, BMS, Amgen, and Merck, and received honoraria from Merck, GSK, and Roche. J. Larkin: Institution received research funding from Pfizer, BMS, MSD, PA. Ascierto received honoraria from BMS, Roche-Genentech, and GSK, served as a consultant for BMS, Roche-Genentech, MSD, GSK, Ventana, Novartis, and Amgen, and institution received research funding from BMS, Roche-Genentech, and Ventana. F.S. Hodi: Served as a consultant from BMS (non-paid), institution received research funding from BMS, and his institution has a patent pending for immune target. P. Rutkowski: Honoraria from BMS, Roche, Novartis, MSD, and GSK, consulted for BMS, Amgen, and MSD, participated in speaker’s bureau for Pfizer, MSD and Novartis, institution received research funding from BMS, and received travel support from Novartis. V. Sileni: Served as a consultant for Roche, BMS, GSK, and MSD, participated in speaker’s bureau for Roche, BMS, and GSK, and received travel support from Roche, GSK, and MSD, and B. Hassel: Received honoraria from BMS, GSK, Roche, and MSD, and served as a consultant for Amgen and GSK, participated in speaker’s bureau for BMS, Roche, GSK, MSD, and Amgen, and received travel support from Amgen and MSD. C. Lebè: Dr. Lebè served on advisory boards for BMS, Roche, GSK, and Novartis. A.C. Pavlick: Served as a consultant for BMS and Amgen, and participated in speaker’s bureau for BMS. J. Wagnall: Served as a consultant from Amgen and MSD. D. Hogg: Served as a consultant from BMS, Roche, Novartis, and GSK, and as a speaker for BMS, Roche, GSK, and MSD, and received travel support from Amgen, MSD, and B. Hassel. F. Schadendorf: Served as a consultant for Roche, MSD, and Amgen, and received research funding from MSD. R. Dummer: Paid honoraria from Roche, BMS, GSK, and MSD, served as a consultant for Roche, BMS, GSK, and MSD, and received research funding from MSD and Roche, MSD, Roche, Amgen, and MSD. C. Hoeller: Paid honoraria from Roche, BMS, MSD, GSK, and MSD, and served as a consultant for Roche, BMS, Roche, GSK, and MSD, and received research funding from Roche, BMS, MSD, and GSK. While pts with high PD-L1 expression ≥5% and <5% PD-L1 subgroups, respectively. The frequency and types of treatment-related grade 3-4 adverse events were consistent with earlier reports (NIVO + IPI: 56.5%, NIVO: 18.2%) and did not differ by PD-L1 expression. Conclusions: While pts with ≥5% PD-L1 tumor expression have better efficacy outcomes, those with <5% PD-L1 expression still benefit from NIVO + IPI or NIVO. Among pts with high PD-L1, mPFS of NIVO + IPI and NIVO were similar, but the ORR of NIVO + IPI was numerically higher across PD-L1 subgroups. As OS data have not yet matured, caution is advised when applying these results to assess the relative benefit of NIVO + IPI vs NIVO. Clinical trial identification: NA

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

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Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases


Background: Patients (pts) with metastatic melanoma and untreated, symptomatic or progressing brain metastasis (BM) have a poor prognosis and have been excluded from the published trials of the anti-programmed death 1 (PD-1) antibodies pembrolizumab and nivolumab; as a result there is limited data on the efficacy and safety of these agents in this cohort of patients. Methods: We retrospectively assessed the efficacy of PD-1 agents in pts with metastatic melanoma with BM treated across four centres. Patient demographics, tumour characteristics, and treatment and imaging data including corticosteroid use were collected. Intracranial (IC) and extracranial (EC) response rates (RRs), progression-free survival (PFS) and overall survival (OS) were calculated. Results: From 2010 to 2014, 86 pts were identified with interim analysis of 39 reported here with median F/U of 8.5 months (95% CI 5.1 to 11.4). 77% pts were male. At PD-1 inhibitor commencement, 56% had an elevated LDH; 64%, 26% and 10% had an ECOG of 0-1, 2 and 3 respectively. Median number of IC lesions was 4 (range 1-20). 26 (67%) had focal treatment (RT or surgery) to BM prior to PD-1 therapy. 23 (59%) were BRAF mutant, 9 (23%) started anti-PD-1 as 1st line therapy. Dexamethasone was used in 13 (33%) pts with dose range of 0.5 – 8mg. The IC RR was 10/39 (26%), including pts with symptomatic BM and pts receiving steroids (see Table). 2/10 IC RR had no prior RT (SRS or WBRT). 3/10 had concurrent RT and 5/10 had prior RT. The EC RR was 6/35 (17%).

Table: 1114PD

<table>
<thead>
<tr>
<th>Best IC response</th>
<th>All pts (N = 39)</th>
<th>Symptomatic BM (N = 10)</th>
<th>Corticosteroids for BM (N = 13)</th>
<th>Radiotherapy prior to or during PD-1 (N = 28)</th>
</tr>
</thead>
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<tr>
<td>CR/PR</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>8</td>
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<tr>
<td>SD</td>
<td>8</td>
<td>5</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>PD</td>
<td>12</td>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Clinical PD (without imaging)</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>4</td>
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</tbody>
</table>

Median IC PFS was 2.1 months (95% CI 1.3 – 2.9) and median EC PFS was 2.1 months (95% CI 1.9 – 3.4). Updated analysis with the full cohort and longer follow up will be presented.

Conclusions: IC responses to anti-PD-1 agents were seen in pts with symptomatic BM and those requiring corticosteroids. Prospective trials evaluating anti-PD-1 therapy in pts with BM are underway, although pts with the poor prognostic features included in this series are unlikely to be represented in prospective trials.

Legal entity responsible for the study: Melanoma Institute Australia, Medical Oncology Department, Westmead Hospital

Funding: Melanoma Institute Australia, Medical Oncology Department, Westmead Hospital

Results: Twenty-four pts were noted to have had a CR and ceased therapy. The median age was 64 (27-83) years. Twenty pts (83%) were BRAF wild type and 4 (17%) pts BRAF mutant. The median number of cycles were 15 on PEM NPP, 18 on NIVO and 11 on r PEM. The median time to CR was 10 months in the PEM NPP, r PEM groups and 17 months in the NIVO group. The median time off therapy in PEM NPP was 7 months, NIVO was 8 months and r PEM was 2 months. To date only one patient from PEM NPP has relapsed and been successfully re-induced.

Conclusions: This is the first report of a cohort of patients who have intentionally ceased PD-1 based therapy because of CR. While the follow up is short as yet only one patient has relapsed off therapy and has been successfully re-induced. Data such as this is both clinically relevant as we need to be able to discuss cessation for CR with our patients and relevant from a pharmaco-economic perspective given the cost of PD-1 antibodies to society.

Legal entity responsible for the study: This has been at the review by the Ethics Committee of Princess Alexandra Hospital.

Funding: N/A

Disclosure: V.G. Atkinson: BMS, MSD, Novartis Advisory Board BMS, MSD, Novartis Speaker fees and travel support. All other authors have declared no conflicts of interest.
The efficacy of nivolumab for unresectable metastatic mucosal melanoma

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Background: As there is no established systemic therapy for unresectable metastatic mucosal melanoma, treatment has been selected on the basis of the available treatment for primary cutaneous melanomas. In Japan, although dacarbazine (DTIC) or DTIC-based combination therapy has been performed, it has been difficult to achieve certain therapeutic outcomes. After nivolumab, an anti-PD-1 antibody, was approved, it was anticipated to be effective against primary mucosal melanomas; however, this remains unclear. This study was conducted to investigate the efficacy of nivolumab against unresectable metastatic mucosal melanoma.

Methods: We retrospectively analysed 27 unresectable metastatic mucosal melanoma cases for which nivolumab had been administered at National Cancer Center Hospital between July 2014 and January 2016. All cases were administered nivolumab (2 mg/kg every 3 weeks) at least three times and therapeutic effects were evaluated according to RECIST 1.1 on the basis of diagnostic imaging.

Results: The subjects included 12 men and 15 women, and the median age was 68 years (48–85 years). The primary onset sites included the nasal cavity (12 cases), esophagus (4 cases), conjunctiva (4 cases), the palate (3 cases), the urethra/nadder (2 cases), and rectum (2 cases). The number of metastasized organs including lymph node metastasis prior to nivolumab administration ranged from 1 to a maximum of 7. The best overall responses were complete response (2 cases: 74%; partial response (7 cases: 25.9%); stable disease (4 cases: 14.8%); and progressive disease (14 cases: 51.9%), resulting in the overall response rate of 33.3%. The response rates for the melanoma of primary onset sites were 25% (3/12 cases) for the nasal cavity, 50% (2/4 cases) for the esophagus, 50% (2/4 cases) for the conjunctiva, 50% (1/2 cases) for the urethra/bladder, 33.3% (1/3 cases) for the palate, and 0% (0/2 cases) for the rectum. The therapeutic effects were still maintained for 8 of the 9 successful cases as of April 2016.

Conclusions: Nivolumab was effective for unresectable metastatic mucosal melanoma as well as for primary cutaneous melanoma. Furthermore, the therapeutic effects were maintained in successful cases.

Legal entity responsible for the study: National Cancer Center Hospital

Funding: National Cancer Center Hospital

Disclosure: N. Yamaizaki: Advisory Board role for Chugai Pharma, Bristol-Myers Squibb (BMS) Japan and Ono Pharmaceutical. The institution has received clinical trial support from Chugai, BMS Japan, Ono, GSK, Takada, AstraZeneca Japan, Boehringer Ingelheim, and Maruh. All other authors have declared no conflicts of interest.

Real-world survival results of metastatic melanoma patients treated with ipilimumab in the Netherlands

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Background: Since 2012 ipilimumab is available for metastatic melanoma patients in the Netherlands. We investigated the survival of this treatment in real-world clinical practice.

Methods: Data were retrieved from the Dutch Melanoma Treatment Registry (DMTR), follow up data cut-off April 14th 2016. This registry records detailed data on tumor and patient characteristics, systemic treatment, grade 3 and 4 adverse events (according to the CTCAE v. 4), outcome and resource use of all patients with unresectable stage IIIc and stage IV melanoma. Kaplan-Meier estimates are used to assess the median overall survival (OS) and survival rates.

Results: From July 2012 until April 2016, 891 patients received at least one cycle of ipilimumab: 458 patients (51%) had received a previous therapeutic regimen. A shift towards applying ipilimumab in treatment naive patients with metastatic melanoma was seen from February 2014 as at that time approval by the National Health Care Institute was obtained for this patient group. Median follow-up was 21 months (95% CI 18.6-23.3) for previously treated patients and 11.3 months (95% CI 10.4-12.3) for treatment naive patients. The median overall survival for previously treated patients was 8.0 months (95% CI 6.8-9.3) with a one year survival rate of 27% (95% CI 32-42) and a two year survival rate of 24% (95% CI 19-28). In this group, patients presenting with normal LDH (71%) had a median OS of 9.9 months (95% CI 8.4-11.5). For treatment naive patients the median overall survival was 14.5 months (95% CI 11.8-17.3) and the one-year survival rate was 54% (95% CI 48-60). Two-year survival rate could not be calculated because the follow-up duration was too short.

Conclusions: The discrepancy between real-world one year survival rates of previously treated patients receiving ipilimumab and pivotal trial results could be due to more stringent patient selection in clinical trials. Inexperience with disease management outside of a controlled clinical trial may have contributed as well. Importantly, two year survival rates for previously treated patients and one year survival rate of treatment naive patients are consistent with patient outcome found in clinical trials with ipilimumab.

Legal entity responsible for the study: Dutch Society for Medical Oncology (NVMO)


1122P Impact of Ipilimumab on metastatic melanoma: Evaluation using patient registry in Canada

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Background: The evaluation of new treatments on patients outside of clinical trials is crucial. The Canadian Melanoma Research Network (CMRN), is a multi-center pan-Canadian registry of melanoma patients. We utilize the CMRN to determine the clinical impact of Ipilimumab (Ipi) as 1st and 2nd line therapy.

Methods: 584 eligible patients, 353 males: 231 females (mean age: 52 yrs), who received Ipilimumab for metastatic disease from 2000 to 2015 were included with their respective follow-up time. For each patient, any line of treatment, 1-year survival rate was 50%, 2-year of 39% and 3-year of 35%. Because Ipi 1st line was introduced after 2nd line, mean follow-up is necessarily shorter.

Results: We divided our cohort into 2 groups, 388 patients who received Ipi and 196 who did not. Baseline characteristics, such as age, gender, performance status, presence of brain metastases for each cohort were similar. From 2011 to 2015, the percentage of patients who did not receive Ipi increased from 68% to 81%. In patients who received Ipi, Cox exhibits a survival rate significantly better (p-value = 0.0010) than patients that were not treated with Ipi. The 3-year survival rate for Ipi treated patients was 32% compared to non-Ipi patients 25%. The survival over time data is available for Ipi patients: 1, 2 and 3 year survival 2011 (32%, 33%, 33%), 2012 (61%, 30%, 49%), 2013 (69, 62%), 2014 (75%), illustrating improved survival rates over time. Patients receiving Ipi 1st line had a 1-year survival rate of 43%, 2-year of 32% and 3-year of 23%. For Ipi given as 2nd line treatment, 1-year survival rate was 72%, 2-year of 47% and 3-year of 33%. For patients who received Ipi as 3rd or more, 1-year survival rate was 70%, 2-year of 49%, and 3-year of 35%. Because Ipi 1st line was introduced after 2nd line, mean follow-up is necessarily shorter.

Conclusion: This observational study illustrates the positive impact that Ipi has had on survival rates. Although the follow-up is still limited, the benefit seems to be incremental as higher proportion of patients received Ipi over time. The efficacy appears to be independent of whether it is given as 1st, 2nd or 3rd line.

Legal entity responsible for the study: Canadian Melanoma Research Network Funding: BMS, Roche, Merck

Disclosure: D.S. Ernst: Advisory Board: BMS, Novartis, Merck, Hoffman-La Roche. T. Petrella: Advisory Board: Merck, BMS, Roche, Novartis, GSK Research Funding: Roche. All other authors have declared no conflicts of interest.

Table: 1123P

<table>
<thead>
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<th>Select AEs, %</th>
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<th>Grade 3-4</th>
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<tbody>
<tr>
<td>Skin</td>
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<td>7</td>
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<tr>
<td>Rash</td>
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<td>4</td>
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<tr>
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<tr>
<td>Diarrhea</td>
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Clinical trial identification: NCT01024231(CA209-004), NCT01844505 (CheckMate 067), NCT01927419 (CheckMate 069)

Legal entity responsible for the study: Bristol-Myers Squibb

1123P Safety profile of nivolumab (NIVO) and ipilimumab (IPI) combination therapy in patients (pts) with advanced melanoma (MEL)

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Background: Cumulative data indicate greater tumor response from the addition of IPI (anti-CTLA-4 antibody) to NIVO (anti-PD-1 antibody) in MEL pts, but with a higher frequency of adverse events (AEs) than observed with either agent alone. The objective of this pooled analysis is to describe the safety profile of NIVO + IPI across MEL studies in which established guidelines for AE management were utilized.

Methods: A retrospective safety review was conducted for three phase 1-3 trials in which all MEL pts who received at least 1 dose of the standard regimen, NIVO 1 mg/kg + IPI 10 mg/kg Q4W, then NIVO 3 mg/kg QW until disease progression or unacceptable toxicity. Analyses included AEs, select (immune-related) AEs, time to onset and resolution, use of immune-modulating agents (IMi) for management of toxicity, and effect of IMi on outcome.

Results: Among 448 pts, median age was 61 (range:18-87) and 25% had ECOG PS > 0. Median duration of follow-up was 13.2 months. Treatment-related grade 3-4 AEs occurred in 55% of pts, and led to discontinuation in 28%. The most frequent treatment-related select AEs of any grade were skin (44%) and gastrointestinal (47%), the most frequent grade 3-4 select AEs were hepatic (17%) and gastrointestinal (16%). Table: 30% developed a grade 2-4 select AE in >1 organ category. Median time to onset of grade 3-4 treatment-related select AEs ranged from 3.1 wks (skin) to 16.5 wks (renal). Excluding endocrine AEs, median time to resolution of grade 3-4 select AEs with IMi from 1.1 wks (renal) to 7.3 wks (pulmonary). Resolution rates for non-endocrine grade 3-4 select AEs ranged between 79–100% using IMi. 4 (1%) deaths were attributed to therapy.

Conclusions: The frequency of grade 3-4 treatment-related AEs was higher with NIVO + IPI and time to onset of select AEs occurred earlier than with either agent alone. Resolution rates of select AEs were similar to those previously reported with IPI monotherapy.
Detailed safety profile of the anti-PD-1 monoclonal antibody pembrolizumab in 78 consecutive patients (pts) with advanced melanoma

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Background: The programmed death receptor 1 (PD-1) inhibitor pembrolizumab has shown clinical benefit with acceptable tolerability in pts with advanced melanoma. We provide detailed information on the safety profile of pembrolizumab in one institution.

Methods: In the KEYNOTE-001 phase 1 trial, pts with advanced melanoma received either pembrolizumab 10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks or 2 mg/kg every 2 weeks until disease progression or severe toxicity. The incidence of adverse events (AEs) was graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.0. AEs were depicted using percentages. The cumulative incidence of AEs from treatment initiation was estimated with the Kaplan-Meier method.

Results: 78 pts received pembrolizumab 2 mg/kg Q2W (n = 23) or 10 mg/kg Q3W (n = 33) in our institution. The median duration of follow-up was 20 months. Treatment was well tolerated, with a cumulative incidence of AEs in pts with the 3 pembrolizumab dosing regimens and no drug-related death. AEs of any grade were observed in 73 pts (94%). The most common AEs were fatigue, asthenia, vitiligo, pruritus and diarrhea. The time to onset of AEs did not differ between the 3 dosing regimens (p > 0.4). The median times to onset of skin disorders and musculoskeletal disorders were 8 months and 17 months respectively. In the median time to onset of gastrointestinal disorders, we did not reach. Grade 3 or 4 AEs occurred in 11 pts (14%). Permanent discontinuation was reported in 7 pts (9%) due to treatment-related AEs, including colitis, thromboembolic events, pneumonitis, interstitial nephritis and hemolytic anemia. Unexpected AEs were reported, including infections in 31 pts (40%), teeth/gingival abnormalities in 8 pts (10%) and pleural effusion in 3 (4%). Vitiligo was reported in 21 pts (27%) and seemed to be associated with pembrolizumab.

Conclusions: This safety analysis provides a detailed characterization of the AE profile of pembrolizumab, and reports new unexpected AEs potentially related to the drug.
Slow natural history predicts higher response rate to nivolumab and pembrolizumab in advanced melanoma patients


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Background: Anti PD-1 antibodies nivolumab and pembrolizumab are checkpoint inhibitors widely used in metastatic melanoma with a 40% response rate. Little is known on predictive factors of response. Given the mechanism of action, we investigated whether features of natural history of melanoma correlated with response.

Methods: All melanoma patients treated with anti PD-1 between August 2014 and January 2016 in our center were retrospectively reviewed. Objective response to treatment was defined as complete response or partial response according to 1.1 RECIST criteria. Patients who received only 1 inclusion were excluded. No clear definition of lymphatic or hematogenous dissemination in melanoma could be found in the literature. We defined lymphatic dissemination as exclusive lymphatic metastases or occurrence of a lymph node metastasis prior to a visceral metastasis. The rest was considered hemogenous dissemination. We excluded patients with only in-transit metastases (stage N2c). Time-in-node was defined as the delay between first lymphatic metastasis and first visceral metastasis. Time-to-treatment was defined as the delay between melanoma diagnosis and anti PD-1 therapy initiation.

Results: 65 patients were included (31 females; median age 65 years [21 to 90]). Treatment was initiated in patients having disease progression. 77% received pembrolizumab and 27% nivolumab. 28% of tumors harbored Braf V600 mutations. Anti PD-1 was the first line therapy for 36% of the patients. Dissemination was lymphatic in 23 patients (37%), and hemogenous in 39 (63%). Objective response rate in the total population was 40%. Mean time-in-node was 26 months [2 to 132 months]. Mean time-to-treatment was 71 months (2 to 409 months). There was no statistical correlation between response and either lymphatic vs hematogenous dissemination or time-in-node. Time-to-treatment was statistically associated with response (mean time-to-treatment 99 months in responders and 53 in non-responders, p = 0.01). The same analysis with time from diagnosis to first line therapy was also positive (57 months in responders and 45 in non-responders, p = 0.02).

Conclusions: Melanomas with slow natural history exhibit a higher sensitivity to nivolumab and pembrolizumab.

Legal entity responsible for the study: Hôpital Cochin APHP

Funding: Hôpital Cochin APHP

Disclosure: All authors have declared no conflicts of interest.

Correlation between baseline characteristics and clinical outcome of patients with advanced melanoma treated with pembrolizumab (PEMBRO)


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Background: Treatment of patients (pts) with advanced melanoma. Correlation between baseline characteristics and outcome of pts treated outside of a prospective clinical trial has not been established.

Methods: Using Kaplan-Meier statistics, log rank testing and multivariate Cox-regression analysis, correlations were investigated between variables and PFS and OS in pts with advanced melanoma who received PEMBRO outside a clinical trial. An independent confirmatory cohort (CC) of pts from the Netherlands and Spain served to confirm correlations found in an exploratory Belgian cohort (EC). Additional data from 180 Scandinavian pts are being collected.

Results: All pts in the EC (N = 123) and CC (N = 165) received at least one administration of PEMBRO (2 mg/kg q3wks). Baseline characteristics of the total cohort (TC) (N = 288) were: median age 60y (range 27-93), 49% male; 61% performance score (PS) 0; primary site: 80% skin, 15% UKN, 4% mucosal; 49% BRAF V600mut; 76% AJCC stage IV-M1c; 29% brain metastases; 82% pretreated; 48% CRP >ULN; 33% LDH >ULN; 16% absolute lymphocyte count (ALC) <1000/mm3. For the TC median PFS was 17 wks (95% 13-19), median OS was not reached. PFS and OS did not differ between cohorts. An inflection point on the PFS curve occurred around 30wks. Age, gender and primary site did not correlate with survival in either cohort. EC pts with stage M1c, PS2, brain metastases, ALC <500/mm3 had a significantly worse PFS/OS. However, only the correlation with PS, LDH and ALC could be confirmed in CC pts. In the TC a significant correlation could be found between PFS/OS and PS2, ALC <500/mm3, M1c stage, CRP >5xULN and LDH and LDH >1.5xULN with a typical "lower PFS plateau" beyond 30 wks. All pts with a baseline ALC <500/mm3 (N = 7; 2.5%) had a PFS and OS of < 9 wks. In pts with ALC >500/mm3 (N = 281), multivariate analysis identified baseline PS2, LDH >1.5xULN and CRP >5xULN as independent unfavorable prognostic factors for PFS/OS.

Conclusions: While confirming encouraging survival outcome of advanced melanoma patients treated with PEBRO outside a clinical trial setting, significant correlations were found between baseline PS, ALC, LDH, CRP and survival.

Clinical trial identification: NCT02673970

Legal entity responsible for the study: UZ Brussel

Funding: UZ Brussel, NKI AVL


CARAMEL study: Clinical prognostic biomarkers for ipilimumab-related outcome in metastatic melanoma patients


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Background: Ipilimumab is an inhibitor of CTLA4 receptor of T lymphocytes approved by the FDA both as a first and second line treatment for patients with metastatic melanoma. Despite the efficacy observed in about 20% of patients, it still remains a therapy with a considerable outcome, both from an economic and safety point of view: the aim of our study was to explore prognostic biomarkers among hematological parameters normally used in clinical practice.

Methods: This is a retrospective multicenter study which enrolled 120 patients with histologically confirmed metastatic melanoma treated with ipilimumab between January 2013 and January 2016 (mean age 62.2 ± 14.58). Full blood count with absolute WBC (aWBC), neutrophil count, eosinophil count, neutrophil/lymphocyte ratio (NLR), platelets/lymphocyte ratio (PLR) and LDH serum levels were assessed at baseline and every 3 weeks during treatment. We evaluated the mutational BRAF status and the number of metastatic sites involved before treatment (more or less than 3 sites). The cut-off values for our parameters were determined with time-dependent receiver operating characteristic (ROC) analysis. To identify prognostic and predictive biomarkers the above parameters have been correlated with Progression-Free Survival (PFS) and Overall Survival (OS).

Results: After a median follow up of 21 months, median PFS was 4 months and median OS was 17 months. Patients with low serum LDH levels at baseline had significantly longer PFS (p = 0.018) and OS (p < 0.05). Higher NLR (p = 0.043) and PLR values (p < 0.05) were related to worse PFS. Interestingly, we found that women had shorter OS (p = 0.002) and PFS (p = 0.003) compared with men. The presence of >3 sites of metastases seems to be correlated to a worse OS (p < 0.04) and PFS (p < 0.03).

Conclusions: Although these findings need to be confirmed and validated and the multivariate analysis is still in progress, we suggest that the parameters explored in our study, which are normally assessed in clinical practice, may be useful to assist disease-management strategies for advanced melanoma patients.

Legal entity responsible for the study: Prof. Mario Scartozzi, AOU Cagliari

Funding: Prof. Mario Scartozzi, AOU Cagliari

Disclosure: All authors have declared no conflicts of interest.
Sarcopenia associated with a body mass index (BMI) ≥ 25 kg/m² predicts severe acute toxicity of nivolumab and pembrolizumab in melanoma patients

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Backround: Anti-programmed cell death protein 1 (PD-1)-monoclonal antibody, nivolumab, is one of the most effective drugs for advanced melanoma. Serum lactate dehydrogenase (LDH) and cutaneous adverse events have been described as early predictors for outcomes of advanced melanoma treated with nivolumab in some literature. We tried to seek further clinical predictors in daily clinical practice.

Methods: We retrospectively analyzed clinical findings of 54 unresectable stage III or IV melanoma patients treated with nivolumab at the National Cancer Center Hospital, Tokyo, Japan, between September 2014 and December 2015. The patients who took steroids orally were excluded from this study. Those patients were administered nivolumab at a dose of 2mg/kg every 3 weeks.

Results: Median overall survival (OS) was 12.7 months. Response rate was 25.9%. Delayed response was shown in only one patient. Patients with baseline ECOC performance status (PS) = 0, baseline normal LDH and baseline normal C-related protein (CRP) had significantly longer OS compared with patients with PS ≥ 1 (hazard ratio [HR] 0.25, 95% CI 0.09-0.68, P < 0.01), elevated LDH (HR 0.25, 95% CI 0.10-0.60, P = 0.010) and elevated CRP (HR 0.36, 95% CI 0.15-0.87, P = 0.018). As for early markers through the therapy, patients with adequate lymphocyte count (ALC) ≥ 1000/mL and neutrophil-to-lymphocyte ratio (NLR) ≤ 4 after 1st nivolumab dose had longer OS significantly compared with those with ALC < 1000/mL (Week1: HR 0.30, 95%CI 0.12-0.78, P = 0.016; Week6: HR 0.38, 95%CI 0.15-0.95, P = 0.000) and NLR ≥ 4 (Week6: HR 0.38, 95%CI 0.18-0.87, P = 0.018; Week12: HR 0.37, 95%CI 0.19-0.72, P = 0.026).

Conclusions: Delayed response may rarely occur in daily clinical practice. ALC ≥ 1000/mL and NLR ≤ 4 during treatment appear to be early markers associated with better OS. Pretreatment PS = 0 and low CRP can also be good prognostic factors as well as low LDH.

Legal entity responsible for the study: National Cancer Center Hospital

Funding: National Cancer Center Hospital

Disclosure: N. Yamaoka: Advisory board role for Chugai Pharma, Bristol-Myers Squibb (BMS) Japan and Otsuka Pharmaceutical. The institution has received clinical trial support from Chugai, BMS Japan, Otsuka, GSK, Takeda, AstraZeneca Japan, Boehringer Ingelheim, and Maruhana. All other authors have declared no conflicts of interest.

More than 50% of patients with metastatic melanoma are not represented in pivotal phase 3 immunotherapy registration trials

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Background: Recent randomized trials with strict patient (pt) selection criteria led to the approval of several immune checkpoint inhibitors for unresectable or metastatic melanoma (MM). It is currently unknown how large is the proportion of real life pts with MM not represented in these trials

Methods: Data from all MM patients referred in 2014 to assessment for systemic treatment were retrieved from the Danish MM Database. Data were available from two of three reference centers, where all pts diagnosed with MM are referred. A total of 194 cases (uveal melanoma was excluded) were retrieved, and 183 pts with sufficient records were included in the analysis. Seven pre-defined enrolment eligibility criteria, all employed in five recent randomized phase 3 immunotherapy trials, were analyzed

Results: At 1 pt visit, the majority of pts (82%, n = 150) had confirmed cutaneous melanoma, 15% melanoma of unknown primary origin and 3% had mucosal melanoma. 32% of the pts had PS ≥ 2, 22% active/untreated known brain metastases; 22% significant comorbidities; 19% other malignancies in the last 5 years; 6% autoimmune diseases and 19% were on treatment with immunosuppressive drugs. 4 additional pts were not eligible because of the absence of target lesions. In total, 59% of the total population did not fulfill at least one enrolment criteria (non-eligible group). Median survival of the non-eligible group was 5.2 months versus 17.3 months for the eligible (p < 0.0001, HR 2.39), reflected by significantly poorer baseline prognostic features. In contrast, baseline characteristics of the eligible group were very similar to the average of patients (n = 3375) enrolled in five recent phase 3 trials. Median survival of the eligible group was comparable to the control group (pembrolizumab) of patients enrolled in Keynote-066 trial, reflecting similar pts characteristics and treatment options.

Conclusions: At least half the patients evaluated for systemic treatment of MM are not represented in phase 3 registration immunotherapy trials. These data reveal a huge...
Methods: The pooled population included randomized pts treated with D 150 mg twice daily + T 2 mg once daily in BRF113220 (Part C; cutoff Jan 2015), COMBI-d (cutoff Jan 2015), and COMBI-v (cutoff Mar 2015). Baseline factors (Table) were analyzed by regression tree analyses to identify predictors of D + T treatment (Ts), PFS, or OS lasting ≥ 24 mo.

Results: Of 617 pts treated with D + T in BRF113220 (n = 54), COMBI-d (n = 211), and COMBI-v (n = 352), 165 (27%) received it for ≥ 24 mo. Long-term PFS (n = 472) and OS (n = 456) analyses excluded pts censored prior to 24 mo. A total of 85 pts (18%) had PFS ≥ 24 mo and 86 (41%) had OS ≥ 24 mo. Table. Regression tree analyses identified baseline lactate dehydrogenase (LDH) as the most predictive factor for durable benefit. Pts with normal vs elevated LDH improved PFS (median 12.1 vs 5.5 mo; 2-y rate: 26% vs 5%) and OS (median: 31.6 vs 10.8 mo; 2-y rate: 56% vs 15%). At data cutoff, 172 pts (28%) remained on D + T, including 140 (81%) with Ts ≥ 24 mo and 69 (40%) with PFS ≥ 24 mo.

Table: 1134P

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PFS &lt; 24 mo</th>
<th>PFS ≥ 24 mo</th>
<th>OS &lt; 24 mo</th>
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<tr>
<td>Age, median, y</td>
<td>55</td>
<td>56</td>
<td>53</td>
<td>57</td>
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<tr>
<td>BRAF mutation, n (%)</td>
<td>V600E</td>
<td>334 (86)</td>
<td>75 (88)</td>
<td>233 (86)</td>
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<td>V600K or V600E and V600D</td>
<td>53 (14)</td>
<td>10 (12)</td>
<td>37 (14)</td>
<td>25 (13)</td>
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<td>Disease stage, n (%)</td>
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<td>42 (49)</td>
<td>60 (22)</td>
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<td>IVM1a, or IVM1b</td>
<td>IVM1c</td>
<td>279 (72)</td>
<td>63 (51)</td>
<td>210 (79)</td>
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<td>ECOG PS, n (%) ≥ 2</td>
<td>258 (67)</td>
<td>66 (57)</td>
<td>155 (58)</td>
<td>96 (52)</td>
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<tr>
<td>Sex, n (%) Female</td>
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<td>59 (66)</td>
<td>95 (33)</td>
<td>50 (27)</td>
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<td>Normal</td>
<td>236 (61)</td>
<td>46 (54)</td>
<td>175 (63)</td>
<td>93 (50)</td>
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<td>LDH, n (%)</td>
<td>215 (56)</td>
<td>78 (89)</td>
<td>124 (46)</td>
<td>181 (87)</td>
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<td>Normal</td>
<td>108 (28)</td>
<td>91 (11)</td>
<td>90 (34)</td>
<td>24 (13)</td>
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<tr>
<td>Prior adjuvant ipilimumab, n (%)</td>
<td>No</td>
<td>391 (98)</td>
<td>86 (92)</td>
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<td>5 (4)</td>
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<td>Prior non-ipilimumab adjuvant therapy, n (%)</td>
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<td>543 (11)</td>
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<tr>
<td>No</td>
<td>216 (56)</td>
<td>26 (34)</td>
<td>174 (64)</td>
<td>66 (35)</td>
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<td>Sum of target lesion diameter, n (%)</td>
<td>&lt; median (58 mm)</td>
<td>218 (57)</td>
<td>28 (33)</td>
<td>171 (64)</td>
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<tr>
<td>≥ median (58 mm)</td>
<td>216 (56)</td>
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<td>174 (64)</td>
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<td>Best Response</td>
<td>Complete response, n (%)</td>
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<td>Partial response, n (%)</td>
<td>122 (35)</td>
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<td>107 (58)</td>
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<td>Stable disease, n (%)</td>
<td>110 (28)</td>
<td>2 (2)</td>
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<td>3 (1)</td>
<td>0</td>
<td>7 (3)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
| ECOG PS, Eastern Cooperative Oncology Group performance status; ULN, upper limit of normal. For all characteristics except ECOG PS (n = 385), LDH (n = 385), and sum of target lesion diameter (n = 385), for all characteristics except ECOG PS (n = 268), LDH (n = 288), and sum of target lesion diameter (n = 267). Any group with ≥ 1 metastasis could be counted as a single organ site.

Conclusions: Long-term Tx and durable PFS and OS were achieved in a subset of pts with BRAF V600-mutant melanoma receiving D + T. Baseline LDH was the strongest predictor for PFS and OS ≥ 24 mo. Additional follow-up analyses are needed to further define the durability of PFS and OS achievable with D + T.

Clinical trial identification: NCT01597908, first received by CT.gov on May 10, 2012 and NCT01584648; first received by CT.gov on April 23, 2012 and NCT01072175; first received by CT.gov on February 12, 2010.

Legal entity responsible for the study: Supported by GlaxoSmithKline. Dabrafenib and trametinib are trademarks of Novartis AG as of 2 March 2015.

Funding: Supported by GlaxoSmithKline. Dabrafenib and trametinib are trademarks of Novartis AG as of 2 March 2015.

Background: Patients (pts) with BRAFV600-mutant advanced melanoma benefit from treatment with the combination of a BRAF- and a MEK-inhibitor. Acquired resistance could potentially be reversible when selective pressure by BRAF-inhibitor is withheld for a sufficient period of time.

Methods: This single-arm, 2-stage, phase II trial addresses the potential renewed anti-tumor activity of dabrafenib (150mg BD) and trametinib (2mg QD) in pts with unresectable BRAFV600-mutant melanoma who are documented with disease progression (PD) at least 12 weeks following the last day of dosing of a BRAF-inhibitor containing treatment regimen, and have experienced PD on immunotherapy. Tumor response rate served as the primary end point. Sample size (25 pts) was calculated according to a two-stage Simon Minimax design. Rechallenge with dabrafenib and trametinib will be considered sufficiently active for further clinical investigation if a confirmed tumor response is documented in at least 4 pts.

Results: Between April 2014 and February 2016, 25 pts were recruited. Baseline characteristics: 15M/10F, median age 64y (range 29-72), AJCC stage IV-M1a/-M1b/-M1c: 1/1/23 pts. Median follow-up time is 6 months (range 1-23), and tumor response was evaluated in all pts. A confirmed PR was documented in 8 pts (32%), SD was observed in 10 pts (40%). Median PFS was 4.8 months (95% CI: 2.8 - 6.8), median OS was not reached. Most frequent treatment related adverse events (AE) were pyrexia in 10 pts (40%), fatigue and myalgia in 7 pts (28%), AST, CK and AP elevation in 6 pts (24%), ALT elevation in 5 pts (20%), panniculitis in 3 pts (12%). Grade 3/4 AE occurred in 3 pts (1x panniculitis, 1x GGT elevation, 1x pyrexia). There were no grade 5 AE.

Conclusions: This phase II trial found that BRAFV600-mutant melanoma who experienced prior progression on BRAF(MEK)-inhibitors, were off BRAF(MEK) inhibitor therapy for at least 12 weeks, and progressed on immunotherapy, benefited sufficiently from rechallenge with dabrafenib and trametinib to warrant further investigation.

Clinical trial identification: EudraCT 2013-004966-33

Legal entity responsible for the study: Sponsor Legal Registered Address: UZ Brussels, Laarbeeklaan 101 1099 Brussels Belgium UZ Gent, Dr Pintelaan 185 9000 Gent Belgium

Funding: Novartis

Disclosure: B. Neyns: Financial compensation from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, AstraZeneca, CryoStorage for public speaking, consultancy and participation in advisory board meetings. All other authors have declared no conflicts of interest.

The most common (% pts) adverse events (AEs)/drug related AEs in the PIM arm were diarrhea (82.3/70.8), elevated creatine kinase (CPK) (68.5/68.5), peripheral edema (46.2/38.5) and serous retinal detachment (44/44.6), % pts with grade ≥3 drug related grade ≥3 of these AEs were 6/23.8, 33/83.3, 2.3/2.3 and 3/1.3, respectively. Ocular AEs in PIM pts were reversible (>92%), mild to moderate (>95%) and did not impact on visual acuity (in >91%). Most (>90%) cases of CPK increase were asymptomatic, transient and reversible laboratory findings.

Conclusions: The primary objective of significant PFS improvement in the PIM arm was achieved. Consistent trend in favor of the PIM arm for PFS, ORR and DCR was seen, but no difference in OS. The safety profile of PIM was consistent with previous studies with no new safety signals.

Clinical trial identification: EudraCT 2012-002669-37

Legal entity responsible for the study: Merck KGaA

Funding: Merck KGaA

Disclosure: C. Lebbe: Member of advisory board for: Roche Novartis Bristol-Myers Squibb MSD. T. Lesimple: Research grants: Roche Advisory board member: Roche Novartis MSD. W. Kruit: Advisory Board Member: MSD Bristol-Myers Squibb. F. Dreno: B. Neyns: Member of advisory board for: Boehringer Ingelheim, Phlogen, Novartis Oncology, ICRS, GlaxoSmithKline, MSD, Bristol-Myers Squibb, Merck Serono, Eli Lilly, Servier, Tusana Life Sciences. C. Garbe: Advisory board member for: Asten Bristol-Myers Squibb MSD Novartis Leo Pharma Research funding from: Bristol-Myers Squibb Roche. C. Loquai: Advisory board member for: Roche Bristol-Myers Squibb Novartis Amsen MSD Speakers honoraria from Roche, Bristol-Myers Squibb Novartis Roche. C. Robert: Advisory board member for: Asten Bristol-Myers Squibb Novartis Merck Roche. R. Isaacs: On board of directors for: Australia New Zealand Breast Cancer Clinical Trials Group. E. Espinosa: Advisory Board Member: Bristol-Myers Squibb Merck Novartis Roche. Roche. A. Schueler, A. Markivskyy: Employed by Merck KGaA. B. Dreno: Member of advisory board for: Roche GlaxoSmithKline Roche Bristol-Myers Squibb. All other authors have declared no conflicts of interest.
Background: D + T improved outcomes and HRQOL in pts with BRAF V600–mutant melanoma vs BRAF alone in COMBI-d (NCT01584648) and COMBI-v (NCT01599708). Although pooled analysis of melanoma clinical/prognostic characteristics across D + T registration trials identified baseline (BL) LDH as the most influential covariate on outcomes, D + T improved response, PFS, and OS vs BRAFi alone in both normal and elevated LDH groups. This retrospective analysis of COMBI-d and COMBI-v patient-reported outcomes (PROs) assessed whether HRQOL was consistently improved across LDH groups.

Methods: COMBI-d and COMBI-v are phase 3, randomized, double-blind studies of first-line D + T vs D + placebo (Pbo) or vemurafenib (V), respectively, in pts with unresectable V600 BRAF–mutant melanoma. HRQOL was evaluated in COMBI-d and COMBI-v by EORTC QLQ-C30 (global QOL, functional, and symptom domains) at BL, during treatment (Tx), and at disease progression (PD). PROs were analyzed by LDH (≤ ULN and > ULN). ANCOVA adjusted for BL score using mixed-model repeated measures was carried out.

Results: Across COMBI-d (D + T, n = 211 [77 with LDH > ULN]); D + Pbo, n = 212 [71 with LDH > ULN]) and COMBI-v (D + T, n = 352 [118 with LDH > ULN]); V, n = 352 [114 with LDH > ULN]), EORTC QLQ-C30 completion rates were > 85% through wk 24. HRQOL was consistently improved across LDH groups.

Conclusions: D + T consistently improved HRQOL vs BRAFi alone for most EORTC QLQ-C30 domains, regardless of LDH, further supporting continued use of D + T in BRAF-mutant melanoma across LDH subgroups. HRQOL benefit with D + T may be greater in pts with LDH > ULN.

Clinical trial identification: NCT01597908, first received by clinicaltrials.gov on May 10, 2012 and NCT01584648, first received by clinicaltrials.gov on April 23, 2012.

Legal entity responsible for the study: Supported by GlaxoSmithKline. Dabrafenib and trametinib are assets of Novartis AG as of 2 March 2015.

Funding: Supported by GlaxoSmithKline. Dabrafenib and trametinib are assets of Novartis AG as of 2 March 2015.

Disclosure: J.J. Grob: Consultancy: Novartis, GSK, Roche, Merck, BMS, Amgen. C. Robert: Consultancy: Novartis, Amgen, BMS, Merck, Roche Honoraria: Novartis, Amgen, BMS, Merck, Roche. G.V. Long: Consultancy: Roche, BMS, Merck, Amgen, Novartis Honoraria: BMS, Merck, Novartis. V. Chiarion-Sileni: Consultancy: Novartis, BMS Speakers Bureau: GSK, Novartis Membership on Board of Directors or Advisory Committee: GSK, Novartis, Roche, BMS, MSD. K. Flaherty: Consultancy: Novartis, Roche, Roche, Array, Lilly, Takeda Research Funding: Novartis. P. Nathan: Consultancy: Novartis Speakers Bureau: Novartis Membership on Board of Directors or Advisory Committee: Novartis, Genentech/Roche, GSK, Sanofi-Aventis, Merck Membership on Board of Directors or Advisory Committee: Novartis, Genentech/Roche, GSK, Sanofi-Aventis, Vaccines: J. Zhang, L. Chen: Employment: Novartis Equity Ownership: Novartis. N. Meyer: Research Funding: Genentech/Roche, GSK, AstraZeneca, Sanofi-Aventis, Merck Membership on Board of Directors or Advisory Committee: Novartis, Genentech/Roche, GSK, Sanofi-Aventis, Vaccines: C. Lebbe: Employment: Roche Equity Ownership: Kite Pharma Honoraria: Novartis. M. Davids: Research Funding: Genentech/Roche, GSK, AstraZeneca, Sanofi-Aventis, Merck.

Background: Given the positive findings from the cobRIM phase III study having assessed cobimetinib plus vemurafenib (C + V) in patients (pts) with BRAF V600 mutation-positive unresectable locally advanced/metastatic melanoma, a Temporary Authorization for Use (TAU) program (pre-approval access to new treatment options where unmet medical need exists) has been settled in France for cobimetinib from 27 April 2015 to 04 Jan 2016.

Methods: Analysis was performed in pts with approved treatment access delivered within TAU. Specific forms had to be completed at C initiation (in combination with V) and monthly after first treatment intake. All adverse events (AEs) had to be reported during pts’ follow-up.

Results: A total of 376 pts had approved early access to the combined therapy (C plus V). Following baseline data were available for 328 pts (87%). Mean age was 57 ± 15 years and 39% were male. A total of 280 pts (89%) had stage IV melanoma (M1a: 30%, M1b: 13%, M1c: 64%) and 79 pts (24%) presented with brain metastasis. During follow-up, 280 AEs were reported in 134 pts (40%), including 208 (74%) C-related AEs reported in 108 pts (29%) and/or 160 (57%) V-related AEs reported in 82 pts (22%). Among the 101 (36%) serious AEs (SAEs) reported in 63 pts (17%), 67 SAEs (24%) were reported in 42 pts (11%) and were assessed as related to C. Twenty-two (6%) AEs (8% reported in 12 pts (3%)) led to permanent C discontinuation. Fifty-three predefined specific AEs (19%) were reported in 49 pts (13%). 23 cases of cutaneous phosphokininase (including 2 SAEs), 12 photosensitivity reactions (7 SAEs), 7 renal detachments (3 SAEs), 7 renal failures (3 SAEs), and 4 left ventricular ejection fraction decreases (1 SAE). No squamous cell carcinoma nor C-related death were reported during follow-up.

Conclusions: These real-life data from this French TAU program are consistent with safety data collected during clinical development program and showed no new safety signal for C when combined with V to treat pts with unresectable or metastatic melanoma.

Legal entity responsible for the study: Roche S.A.S

Funding: Roche S.A.S

for Adrian Gocan: He is doctor in drug monitoring for Roche S.A.S. M. Mouri: Financial interest for Mehdi Mouri: He works for Roche S.A.S he is doctor and medical responsible in dermatology and hematology. A. Bardet: Financial interest in Melanoma for Aurelie Bardet: She is Bio-statistician for Roche S.A.S M. Moreau: Project manager for Roche S.A.S. M. Mouri: Financial interest for doctor Christina Mateus in melanoma with other Pharmaceuticals companies - Roche

Analysis of patient-reported outcomes by disease progression status in patients (pts) with BRAF V600-mutant metastatic melanoma in the COMBI-d and COMBI-v trials

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Background: Dabrafenib (D) + tremetinib (T) improved efficacy and better maintained health-related quality of life (HRQOL) vs BRAF inhibitor monotherapy in 2 phase 3 trials of pts with BRAF V600-mutant metastatic melanoma. COMBI-d (D + T vs placebo) and COMBI-v (D + T vs vemurafenib). Here, we examine the association of tumor response with HRQOL and symptom scores in COMBI-d and COMBI-v.

Methods: COMBI-d and COMBI-v are randomized, double-blind 3 phase 3 trials in pts with unresectable BRAF V600-mutant metastatic melanoma. The EORTC QLQ-C30 was used to assess HRQOL and symptom scores at baseline and during treatment. Treatment arms in each study were pooled and analyzed by best response (complete response (CR)/partial response (PR)/vs stable disease (SD)/progressive disease (PD)). Maximum improvement (MI) was defined as maximum improvement from baseline in functional domains and maximum decrease in symptom scores. P-values were calculated by 2-sample t test.

Results: In COMBI-d (N = 423; CR/PR, n = 236; SD/PD, n = 184) and COMBI-v (N = 704; CR/PR, n = 417; SD/PD, n = 250), completion rates allowed mean MI scores to be calculated for > 98% of pts. In COMBI-d, pts with CR/PR had greater mean MI (Dabrafenib and trametinib) vs pts with PD (HRQOL vs PD in the global health dimension (13.8 vs 7.5; P = .004) and all functional domains (risk [10.2 vs 7.9; P = .425], social [10.3 vs 6.2; P = .112]; emotional [15.4 vs 10.3; P = .018]; physical [6.9 vs 5.3; P = .664]; cognitive [4.9 vs 1.9; P = .070]). Pts with CR/PR also had greater MI in most symptom scores vs pts with SD/PD, including > 5-point improvements in pain (P = .034) and insomnia (P = .065).

Conclusions: Pts with a response had a greater MI from baseline in HRQOL and symptom scores vs pts without a response, demonstrating the association between tumor shrinkage and HRQOL in COMBI-d and COMBI-v.

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Prognostic subgroups and impact of treatment for post-progression overall survival (ppOS) in patients with BRAFV600E-mutated metastatic melanoma treated with dacarbazine (DTIC) or vemurafenib (VEK) ± cobimetinib (COBII): A pooled analysis

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Background: A pooled analysis of pts treated with DTIC, VEM, or COBI + VEM in the BRIM-2, BRIM-3, BRIM-7, and cobRIM studies was performed to identify pt subgroups prognostic for ppOS, defined as time from progression (PD) to death from any cause. The impact of post-progression treatment (pTx) on ppOS was also assessed.

Methods: All eligible pts with PD were included. Recursive partitioning for censored response variable in a conditional inference framework was performed to model relationships between prespecified covariates (at baseline or PD, initial treatment, and pTx) and ppOS. Identified subgroups were applied to pooled treatment cohorts (DTIC, VEM, or COBI + VEM). A pooled analysis of pts treated with DTIC, VEM, or COBI + VEM in the BRIM-2, BRIM-3, BRIM-7, and coBRIM studies was performed to identify pt subgroups prognostic for ppOS, defined as time from progression (PD) to death from any cause. The impact of post-progression treatment (pTx) on ppOS was also assessed.

Results: A pooled analysis of all pts (N = 809), baseline lactate dehydrogenase (LDH) level (normal, elevated [≤ upper limit of normal [ULN], or >2× ULN), Eastern Cooperative Oncology Group performance status (ECOG PS) at PD (0 vs >0), baseline disease stage (IIIC/M1a/M1b vs M1c), and pTx and IT/TT vs other) were significant prognostic factors for ppOS, producing 7 pt subgroups. Among all pts, 169 received IT (ipilimumab in 96%), 32 received TT, and 608 received other pTx. After adjusting for other covariates (including initial treatment), pTx with IT/TT was associated with longer ppOS. Pooled data for all pts, VEM and DTIC cohorts are in the Table. ppOS data for the COBI + VEM cohort were immature, but followed a similar pattern.

Conclusions: A combination of LDH, disease stage at baseline, pTxR, and ECOG PS at PD identified 7 pt subgroups prognostic for ppOS. After adjusting for other covariates, pTxR was associated with ppOS, with similar results in DTIC and VEM cohorts.

Legal entity responsible for the study: P. Hoffman-La Roche, Ltd.

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Molecular profiling can identify potentially targetable mutations and facilitate treatment decisions. Recently BRAF mutant cell free DNA (cfDNA) was shown as an outcome predictor for melanoma patients on BRAF inhibitors (BRAFi). In this study we explore the potential of next generation sequencing (NGS) to show molecular characterization tissue and plasma monitoring of outcome: the MOBILY study.

Results: Tissue and plasma samples were analysed for concordance from 43 metastatic melanoma (MM) patients (20 men 23 women, med age 62 yrs, 36 cutaneous 4 mucosal 2 ocular). Mutations were detected in 9 genes (BRAF 27, NRAS 3, KIT 2, GNAQ 1, KRAS 1, MAP2K1 1, MCR1 3, CDKN2A 2, p53 1, AKT1 1). Five patients had >1 mutation detected. A young patient with highly resistant MM had 4 simultaneous mutations (2 in resistance genes MAP2K1 and KRAS). Mutatioinal concordance tissue: plasma was 72% (BRAF, NRAS). Seven patients with BRAF mutant MM in long remission with BRAFI had undetectable cfDNA mutational loads. Serial plasma samples were analysed from 3 BRAF mutant patients currently on BRAFI and 1 BRAF mutant patient on immune checkpoint inhibitor (IO). BRAFi allele load dramatically reduced to undetectable levels at 1st month of BRAFI, almost one month before radiological response. Interestingly, significant reduction of mutation levels were detected at 1 clinical month. Further patient analysis will be presented.

Conclusions: NGS tissue profiling is clinically relevant for melanoma providing prognostic information and cfDNA monitoring by NGS is feasible. In our population, serial plasma mutation assessment was in agreement with the clinical course and should be further explored as a monitoring tool of outcome.

Legal entity responsible for the study: Metropolitan Hospital Scientific & Ethics Institutional Board

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A phase 2 study of glembatumumab vedotin (GV), an antibody-drug conjugate (ADC) targeting gpNMB, in advanced melanoma


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Background: gpNMB is an internalizable transmembrane glycoprotein expressed in many tumor types including melanoma. The ADC GV (CDX-011) delivers the potent cytotoxin MMAE to gpNMB+ cells. GV has shown promising activity in advanced melanoma and breast cancer (Ott JCO 2014; Yardley JCO 2015).

Methods: In this Phase 2 single-arm study (CDX011-05), efficacy and safety of GV (1.9 mg/kg q3w) is assessed in advanced melanoma patients (pts) with disease progression after ≤1 chemotherapy, ≤1 checkpoint inhibitor, and if BRAF mutation ≥1 chemotherapy, ≤1 BRAF or MEK + BRAF inhibitor. gpNMB expression is determined retrospectively by central IHC on archival tumor and/or pre-treatment tumor biopsy. Primary endpoint is objective response rate (ORR) (RECIST 1.1) with 26 responders out of 52 evaluable pts as threshold for determining statistical positive outcome. Additional endpoints include progression free survival and overall survival (PFS, OS) (95% CI), duration of response (DOR), safety, pharmacodynamics, pharmacokinetics, and correlation of outcome with gpNMB expression.

Results: Enrollment (n = 62) completed in April 2016: median age = 67 years; 55% male; 21% BRAF mutation; 53% ≥2 lines prior therapy. Preliminary tumor response data (n = 57 evaluable; 5 pts pending 1st response assessment); 1 complete response (CR) and 7 partial response (PR [current confirmed ORR = 14%]); 1 single time-point PR, 26 stable disease (SD) (duration 6-61+ weeks, 11 ongoing). Thus, 50/51 evaluable pts had gpNMB+ tumors, and 38/51 had 100% of epithelial cells gpNMB+. Toxicities include rash, alopecia, fatigue, neuropathy, nausea, neutropenia, decreased appetite and diarrhea; rash may correlate with efficacy.

Conclusions: GV has shown promising activity including induction of partial and complete responses in patients with heavily pre-treated melanoma. The safety profile is manageable and consistent with cytotoxic treatment. DOR, PFS, OS, and correlation of biomarkers with outcome will be analyzed on the mature dataset. An additional cohort will be treated with GV in combination with vemurafenib, an activating anti-CD27 monoclonal antibody, in order to evaluate safety and efficacy of the combination.

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Legal entity responsible for the study: Celldex Therapeutics, Inc.

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A phase I, open-label study of pasireotide in patients with BRAF- and NRAS-wild type, unrespectable and/or metastatic melanoma

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Background: Somatostatin receptors (SSTR) and insuline-like growth factor receptors (IGFR) have been shown to be strongly expressed in melanoma cells. This phase I study evaluated the preliminary safety, pharmacokinetics (PK), and efficacy of pasireotide, a somatostatin analogue with broad SSTR affinity, in patients (pts) with BRAF- and NRAS-wild type, confirmed unrespectable and/or metastatic melanoma.

Methods: Patients (planned N = 18) with unrespectable (stage III) and/or metastatic (stage IV) melanoma and confirmed unrespectable and/or metastatic Merkel cell carcinoma (MCC) were eligible. The study was divided into 3 phases: screening, intra-patient dose-escalation (8 weeks), and follow-up (6 months). The primary endpoint was safety during the 8-wk escalation phase. Secondary endpoints included safety at study completion, disease control rate (DCR, by CT or MRI per RECIST 1.0), PK, effect of pasireotide on biomarkers.

Results: The study was terminated early due to slow recruitment after 2 years (y) from study initiation. Of the 10 melanoma pts enrolled, 50% completed the dose-escalation phase and entered follow-up. Median age: 71.5 y (range, 60-77); 26 y (70%) pts; 8 (38%) males. Median duration of exposure: 6.71 wks (range, 1.6-8.1) for escalation phase, 7.57 wks (range, 4.25-9.7) for overall. Most frequent adverse events (AEs) during escalation phase in ≥ 20% (20%) pts were: diaphoresis (50%), nausea (50%), fatigue (50%), asthenia (50%), anemia (35%), vomiting (35%), diarrhea (30%), hypotension (20%), pyrexia (20%), hypertension (15%), headache (15%), hypertension (15%), nausea (15%), vomiting (15%), anemia (15%), asthenia (15%), anemia (15%), anemia (15%), anemia (15%), anemia (15%). Best overall response rate was 10%. PK exposures increased with increasing dose. Low levels of tumor biomarkers were consistently observed in pts with response (PR or SD).

Conclusions: In pts with BRAF- and NRAS-wild type melanoma, pasireotide is well tolerated and its safety profile is consistent with prior reports in other indications with the exception of lower frequency of hyperglycemia. Preliminary anti-tumor efficacy of pasireotide is encouraging. Pasireotide may be a candidate for combination therapy in advanced melanoma.

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Legal entity responsible for the study: Novartis Pharmaceutical Corporation

Funding: Novartis Pharmaceutical Corporation

Disclosure: R. Dummer: Research funding from Novartis, Merck Sharpe & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, GlaxoSmithKline (GSK), and has a consultant or advisory board relationship with Novartis, MSD, BMS, Roche, GSK, and Amgen outside the submitted work. O.A. Micheli: Has a consultant or advisory board relationship with Bristol-Myers Squibb, Merck Sharpe & Dhome, Roche, and Novartis. F. Campigotto: Has employment and stock ownership with Novartis and has receives research funding from Novartis. J. Kriemler-Krah: Has employment and stock ownership with Novartis. H. Schmid: Has employment and stock ownership with Novartis. A. Pedroncelli: Has employment with Novartis. D. Schadenfroed: Institution receives research funding from Bristol-Myers Squibb (BMS) and Merck Sharp & Dhome, and he has a consultant or advisory board relationship with Amgen, Bristol-Myers Squibb (BMS), Merck, Merck Sharpe & Dhome, Pfizer, Novartis and Roche. All other authors have declared no conflicts of interest.

Chemotherapy in patients with metastatic melanoma after progression on BRAF/MEK inhibitors

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Background: Metastatic melanoma remains a disease with poor prognosis even in patients with BRAF mutation, treated by BRAF/MEK inhibitors. In many countries immune checkpoints inhibitors which could be used for 2nd line treatment are not registered, or not reimbursed. At the same time, experimental evidence supports enhancing the effectiveness of chemotherapy after blocking the MAP-kinase pathway. We evaluated the immediate effectiveness of chemotherapy in patients after progression or intolerance on BRAF/MEK inhibitors.

Methods: We conducted a retrospective analysis of all patients (pts) who received paclitaxel 175 mg / m2 day1 + carboplatin AUC = 5 day 1 (PC) from January 1 to March 30 2016 (n = 35). Group 1 (n = 26) was treated with BRAF / MEK inhibitors (vemurafenib, dabrafenib, trametinib, encorafenib or binimetinib) before PC, group 2 (n = 9) received no inhibitors of BRAF / MEK prior to PC.

Results: Both groups did not differ in demographic characteristics (mean age 52.5 ± 12.4 years in group 1 and 53.7 ± 11.6 years respectively, p = 0.5, males 46.1% and 58.6% respectively, p = 0.78), the primary tumor origin (Unknown 15% and 17.2% respectively, skin 85% and 81.8% respectively (p = 0.5), or the tumor stage at the start of chemo (III unrespectable 7.7% and 0%, IV M1a 11.5% and 13.6%, IV M1b 15.4% and 18.2%, IV M1c 65.3% and 68.2%, respectively, p = 0.5). BRAF mutations rate was higher in Group 1 (96.2% vs 24.1%, p < 0.05). NRAS mutations rate did not differ between groups (18% and 13.8% respectively, p > 0.05). Best overall response rate was calculated (Table 1). The median time to progression in Group 1 was 16 weeks (95% CI 6.12 to 23.87 months) and 7.0 weeks (95% CI 5.17 to 8.28) in Group 2; p = 0.019, HR = 2.14 (95% CI 1.08 to 4.21). The median overall survival can be calculated correctly due to short follow-up (median 28 weeks).

Table: 1145P Best overall response rate

<table>
<thead>
<tr>
<th>Group 1, n (%</th>
<th>Group 2, n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (14)</td>
<td>0 (0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PR (10 (38)</td>
<td>1 (3.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>OR (11 (42)</td>
<td>1 (3.4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>SD (5 (19)</td>
<td>3 (10.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PD (10 (38)</td>
<td>25 (86.5)</td>
<td>p = 0.007</td>
</tr>
</tbody>
</table>

Conclusions: MAP kinase pathway inhibition could enhance effectiveness of subsequent chemotherapy with PC. To evaluate the clinical significance of this observation further studies are needed.

Legal entity responsible for the study: Igor Samoylenko

Funding: N.N Blokhin Russian Cancer Research Center

Disclosure: I.V. Samoylenko: Consultant at BMS, MSD, Novartis. G. Kharkievich, L.V. Derridov: Consultant at Roche, MSD, BMS, Novartis.

Use and clinical impact of conventional cytotoxic chemotherapy (CTx) subsequent to immunotherapy in metastatic melanoma


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Background: In recent years the treatment of metastatic melanoma (MM) has changed drastically with the introduction of immunotherapy (ITx) and targeted therapies. Only a minority of patients (pts) achieve a durable response to such treatments and CTx still has a significant ongoing role to play in the palliative treatment of MM in clinical practice. We aimed to assess the use of CTx in clinical practice since the introduction of ITx and its impact on pts outcome.

Methods: A retrospective database was constructed of all MM pts treated in our institution with ITx between 2011 and 2015 by the systematic cross-match of the Pharmacy and Medical Oncology archives. We then identified pts who received any type of CTx after at least one line of ITx. Objective response rate (ORR) and clinical benefit rate (CRR, including pts with SD for at least 3 months) were assessed using RECIST 1.1 criteria. Overall survival (OS) post ITx and post CTx were calculated.

Results: Sixty-four pts were treated with ITx between 2011 and 2015. 17 pts (27%) received any type of CTx post ITx. All pts had documented progressive disease when commenced on CTx. CTx pts characteristics: male 18 (59%), female 7 (41%), median age 60 (range 27-72), primary cutaneous 21 (64%), ocular 6 (18%). BRAF V600 mutation pos 4 (23%), ipilimumab-pretrated 16 (94.1%), ipilimumab and anti-PD1-pretrated 4 (23.5%). All BRAF positive pts received BRAF and/or MEK inhibitor in addition to ITx. CTx included single-agent DTIC 8 (47.1%), platinum salts-based poly-CTxs 9 (52%). Median OS from commencement of CTx was 11 months (range 2-26). ORR (6/17) was 35.3%. CRR (7/17) was 41.2%. CRR in pts who received one vs two lines of ITx was 4/12 (38.5%) vs 3/4 (75%).

Conclusions: Our analysis shows that in real-world clinical practice about one third of MM pts are still treated with CTx after failure of ITx. Although limited by small numbers and retrospective design, the observed ORR/CRR in our cohort of unselected MM pts suggest that CTxs after failure of ITx might have greater activity than in historical series. We are studying the molecular profile of these pts tumours in order to identify potential predictors of improved CTx benefit.

Legal entity responsible for the study: The N/A

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Evaluation of the pharmacokinetic (PK) profile of vismodegib (Vismodegib) in patients (pts) with multiple basal cell carcinomas (BCCs) across two intermittent treatment regimens in the MIKIE study

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Background: Vismodegib is a first-in-class Hedgehog pathway inhibitor approved for the treatment of adult pts with advanced BCCs. Pts with multiple BCCs, including those with BCC nevus syndrome, require long-term treatment with Vismodegib; however, continuous treatment may not be optimal over extended periods due to risk of chronic low-grade toxicity. MIKIE (NCT01813840) was designed to assess the efficacy and safety of two long-term intermittent Vismodegib dosing regimens in pts with multiple BCCs.

Methods: Pts with ≥1 histopathologically confirmed BCC and ≥6 clinically evident BCCs were randomized in a 1:1 ratio to receive Vismodegib 150 mg once daily on one of two intermittent schedules for 72 weeks: Vismodegib for 12 weeks alternating with placebo for 8 weeks (Regimen A), or Vismodegib for 24 weeks followed by placebo for 8 weeks alternating with Vismodegib for 8 weeks (Regimen B). The primary end point was ≥75% regression of BCCs from baseline to Week 73. At selected sites, samples for PK analysis were obtained at pre-dose and 2 hours post dose at Week 13, and at pre-dose at all subsequent visits. PK outcomes measured included an average of total and unbound Vismodegib from total and unbound Vismodegib.

Results: A total of 229 pts were randomized to Regimen A (n = 116) or Regimen B (n = 113). At a clinical cut-off of 72 weeks, the primary outcome was met. At the interim analysis of the primary outcome, the 2 × 2 factorial design was stopped early. Interim analyses for PK were presented in a preplanned interim analysis of the primary outcome. The PK analysis population included all randomized pts who received ≥1 dose of study treatment and had at least one PK assessment.

Conclusion: The reduction in total number of clinically evident BCCs at Week 73 demonstrates that intermittent Vismodegib dosing schedules are effective in pts with multiple BCCs. The PK analysis of the MIKIE study will characterize the PK profiles for each dosing regimen and will be helpful in informing PK modeling to further optimize the dosing schedule.

Clinical trial identification: NCT01813840

Legal entity responsible for the study: Roche-Genentech

Funding: Roche-Genentech


Subgroup analysis of patients (pts) with Gorlin syndrome treated with vismodegib (Vismodegib) in the STEVIE study

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Background: Vismodegib, a first-in-class Hedgehog pathway inhibitor, is approved (US and EU) in adults with locally advanced BCC (lABC) or metastatic BCC (mBCC). STEVIE (ClinicalTrials.gov NCT1367665), is evaluating safety and efficacy of Vismodegib in pts with advanced BCC, including pts with Gorlin syndrome, a hereditary condition characterised by multiple BCCs. Data from the subset of Gorlin pts in the primary studies are presented.

Methods: Pts with Gorlin syndrome could enrol in the study if they met protocol-defined criteria for lABC or mBCC. Pts received oral Vismodegib 150 mg/day until progressive disease, unacceptable toxicity, or withdrawal. The primary outcome was safety. Secondary outcomes included efficacy and quality of life.

Results: The analysis includes 219 Gorlin pts (lABC, n = 214; mBCC, n = 5) with a median age of 52 (range 18–88) years. Median treatment duration was 374 days and median dose intensity was 85.8%. At cut-off (March 16, 2015), all Gorlin pts experienced ≥1 treatment-emergent adverse event (TEAE). Most common TEAEs were muscle spasm (78.1%), alopecia (78.1%), dysgeusia (58.0%), diarrhoea (30.6%), nausea (23.3%), fatigue (23.3%) and asthma (20.5%). Most TEAEs (56%) were grade 1–2 and serious TEAEs were reported in 17.8% of pts. Treatment discontinuation due to TEAEs occurred in 29.2% of pts and included muscle spasms (8.2%), alopecia (6.8%) and dysgeusia (5.0%); most were grade 1–2 (20.6%). Five pts (2.3%) died due to grade 5 AEs (n = 4) and other reasons (n = 1). All grade 5 AEs presented with confounding factors and assessed as unrelated to Vismodegib per investigator. Best overall response (Response Evaluation Criteria in Solid Tumours version 1.1; investigator assessable cut-off) was 81.7% (95% confidence interval [CI] 75.8–88). Median time to response was 2.9 months (95% CI 2.8–3.7). Median progression-free survival was 32.5 months (95% CI 29.4–not estimable [NE]). Median duration of response was 28.8 months (95% CI 24.8–NE).

Conclusions: TEAEs reported in Gorlin pts are similar to those observed in previous studies of Vismodegib. The results confirmed clinical efficacy of Vismodegib in Gorlin pts, and support the use of Vismodegib in this pt population.

Clinical trial identification: NCT01367665

Legal entity responsible for the study: Roche-Genentech

Funding: Roche-Genentech

Disclosure: N. Basset-Seguin: Employment: Genentech Consultant/Advisory: Novartis, Roche, Leo Pharma, Galderma, Pierre Fabre Patents, Royalties, Other: Genentech Travel; Consulting/Advisory, Roche, Novartis, MerckSerono, Meda-Pharma, MerckSerono, Roche, Menarini, Novartis, Roche-Genentech. R. Kunstfeld: Honoraria: Roche, Novartis Speaker Bureau: BMS, GSK, Roche Pharma Trial Grants/Research Funding: Aven, BMS, GSK, MSD/Merck, Novartis, Roche Pharma; B. Dreno: Consultant/Advisory: Roche, BMS, GSK, Novartis, Roche; Roche Pharma Consulting/Advisory Role: Roche, Novartis, Menarini, Meda-Pharma, Spirig, Leo Pharma; L. Mortier: Honoraria: GSK, Roche, BMS, GSK, Novartis, Roche, Merck; Roche Pharma Consulting/Advisory: Roche, BMS, GSK, Novartis, Roche, Merck; Roche, Novartis Speaker Bureau: BMS, GSK, Roche Research Bureau: Roche, BMS, GSK, Roche, MSD, JSDIN, Roche, Roche Possay, Leo, Spirig Bur: Roche, BMS, MSD, JSDIN, Roche La Possay, Leo, Almirall, Novartis; Therarch: Roche, BMS, Merck, MEIDA, LA Roche Possay, Leo, Almirall, Novartis, GSK, Merck, Roche, Hoffmann-La Roche. I. Kyongh: Consulting/Advisory, Roche, Novartis, Menarini, Meda-Pharma; S. Puig: Roche, Novel, Meda-Pharma, Spirig, Leo Pharma Honoraria: Roche, Novartis, Menarini, Meda-Pharma. All other authors have declared no conflicts of interest.
EHESS: Evaluation of real world treatment outcomes in patients with metastatic Merkel cell carcinoma (MCC) following second line chemotherapy

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Background: MCC is a rare, cutaneous, neuroendocrine tumor. MCC is an aggressive disease associated with frequent locoregional recurrences and visceral metastases, and a high mortality rate. This retrospective observational study aimed to assess treatment outcomes among second line (2L) or later chemotherapy in a real-world setting to better understand treatment pathways and prognosis in distant metastatic MCC patients (pts).

Methods: Data consisted of anonymized pt level information, extracted from a MCC specific registry in Europe. This registry contains data collected from 36 clinical sites in 3 countries (Germany: 53, Austria: 2, and Switzerland: 1). Endpoints described for the study population included objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), durable response rate (DRR) and overall survival (OS). Best overall response was assessed using data from real-world practice provided by physicians to the registry, and thus based on routine radiology data and clinical judgment instead of Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Results: Of the total 971 pts with MCC in the registry, 326 pts were diagnosed with locally advanced or metastatic disease. Thirty four pts were identified with distant metastatic MCC and received 2nd or later line chemotherapy were included. Of these 34, 29 were eligible for the subgroup analysis of immunocompetent pts. Of the 5 immunocompromised pts, four had a B-cell chronic lymphocytic leukemia (B-CLL) and one received immunosuppressive treatment. Among all pts, 64.7% were male and the mean age of this cohort was 64.4 years. ORR to 2L or later chemotherapy was 8.8% (3/35). The median PFS from chemotherapy initiation was 3.0 months, median OS was 5.3 months and median DOR was 1.9 months. The 6-month DRR was 9% and PFS rate was 2.9%. Results in the immunocompetent pt subgroup were consistent with those in the entire population.

Conclusions: Both response rate and duration of response are very poor for 2L or later chemotherapy in distant metastatic MCC pts. Chemotherapy in the second line appears to be most useful for palliation in symptomatic pts. New treatment approaches with dual or triple therapy regimens are needed.

Legal entity responsible for the study: EMD Serono and Merck KGaA

Funding: EMD Serono and Merck KGaA


VISMONEO - a phase II study assessing vismodegib in the neoadjuvant treatment of locally advanced basal cell carcinoma - Patients characteristics


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Background: The neoadjuvant administration of vismodegib in unresectable locally advanced basal cell carcinoma (laBCC) may reduce tumor size, facilitate resection and potentially preserve the functional and the aesthetic aspect of the affected area. VISMONEO is conducted to assess the efficacy and safety of vismodegib in the neoadjuvant treatment of laBCC.

Methods: VISMONEO is an open-label, non-comparative, multicenter, phase II study. Patients (pts) with at least one histologically confirmed laBCC and lesion with a diameter ≥ 2 cm in zones at intermediate risk of tumor recurrence and a BCC with a diameter of ≥ 2 cm in the zones at higher risk of tumor recurrence are included. Oral vismodegib 150 mg once-daily is administered for a maximum of 10 months. A total of 55 expected pts will be followed for 3 years. The primary endpoint is the percentage of BCC pts with tumor down-staging following surgical resection after at least 4 months of vismodegib. Secondary endpoints include clinical benefits assessed by an independent panel of experts; medico-economic impact of this neoadjuvant strategy, safety (NCI-CTCAE, v4.0) and quality of life (Skindex-16 questionnaire).

Results: Between November 2014 and June 2015, 55 pts have been included in 17 centers in France. Half of pts are men (51%), their mean age is 72 years (SD±12) and 73% (n = 40) are ≥ 65 years old. 58% (n = 32) have an ECOG performance status of 0, 35% (n = 19) ECOG1 and 7% (n = 4) ECOG ≥ 2. Disease is measurable in all pts and 3 (5.5%) pts have a Gorlin syndrome. BCC sites are mainly eye (35%; n = 19), ear (14%; n = 8), temporal (14%; n = 8), nose (13%; n = 7), forehead (11%; n = 6), cheek (5%; n = 3), scalp (4%; n = 2), and others (ipsilateral, p<0.05). No previous radiotherapy for most pts 98% (n = 54). In December 2015, 8 pts were still under treatment and 47 completed the protocol (including pts still followed-up and pts resected with a less heavy surgery than planned and a complete response).

Conclusions: The characteristics of patients with laBCC treated with neoadjuvant vismodegib and surgical resection are consistent with the few resectable laBCC patients included in clinical trials. This phase II study is ongoing.

Legal entity responsible for the study: N/A

Funding: Roche

Disclosure: N. Basset-Seguin: Roche, Galderma, Novartis, Leo, Pierre Fabre, Genentech. P. Saiag: S. Dalac-Rat: Roche, IMS, GSK, MSD, Novartis. D. Meddour: abbvie, Algenea. M. Dib: Libre University Hospital. A. Mahmoudi: Roche. All other authors have declared no conflicts of interest.

Clinical trial identification: EudraCT 2013-004338-13

CONVERCE: evaluation of cobimetinib and vemurafenib combination treatment in patients with brain metastases from BRAFV600 mutated melanoma

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Background: Brain Metastases (BM) occur in 10 to 20% of patients (pts) at initial diagnosis of metastatic melanoma (MM) and develop in up to 73% of pts with MM. BRAFV600E mutations are found in around 50% of cutaneous melanomas. Vemurafenib, a BRAF inhibitor, is a standard 1st-line treatment of BRAFV600 MM in Europe, and recent data suggest a benefit for patients with BM. Resistance to a monotherapy with a BRAF inhibitor is frequent. Results of a phase II trial comparing vemurafenib + cobimetinib (MEK inhibitor) to vemurafenib in pts with BRAF mutated BM showed improved PFS and OS. Patients with symptomatic BM were excluded from this study. The objective of CONVERCE, a phase II interventional study, is to determine whether the combination of vemurafenib + cobimetinib is effective in the treatment of BRAFV600 mutated melanoma with BM.

Trial design: Pts with histologically confirmed metastatic cutaneous melanoma, mucosal melanoma, or melanoma of unknown primary origin, and BM for which surgical resection is not feasible will be included. Pts will be treated with vemurafenib 960 mg PO, twice daily from D1 to D28, continuously, and cobimetinib 60 mg PO, once daily, from D1 to D21 (cycle = 28 days) until progression (intracranial or extracranial), unacceptable toxicity, withdrawal of consent, death or decision of the investigator. The primary endpoint is the complete or partial intracranial response rate in cohort A based on the evaluation of patient’s best tumor response assessed by the centralized review committee according to modified RECIST 1.1 criteria. Secondary endpoints include objective intracranial response rates in cohorts B and C; intracranial duration of response, progression-free survival, overall response rate and overall survival in all cohorts; safety; pharmacokinetic study including cerebrospinal fluid, kinetic study of BRAF mutation rate in circulating tumor DNA; pharmacogenetics study. Preliminary results are expected in 2018.

Clinical trial identification: NCT02537600

Legal entity responsible for the study: N/A

Funding: Roche

Disclosure: T. Lesimple: Roche, IMS, GSK, BMS, Novartis, MSD. A. Mahmoudi: Roche, C. Lebbe: Roche, IMS, Novartis, MSD, Agen. All other authors have declared no conflicts of interest.
Phase Ib study of intratumoral oncolytic coxsackievirus A21 (CVA21) and pembrolizumab in subjects with advanced melanoma

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Background: Pembrolizumab is a programmed death receptor-1 (PD-1) blocking antibody that has demonstrated overall and durable response rates in advanced melanoma patients, although less than half of treated patients respond. Therapeutic responses have been associated with tumor expression of PD-L1. Oncolytic viruses are live viral particles that can be injected into tumors resulting in lysis of tumor cells, release of tumor-associated antigens and increased expression of PD-L1. Coxsackievirus A21 (CVA21) is a native oncolytic virus that in phase I and II studies has been safe and well-tolerated with an overall response rate of 28.1% and a 1-year survival rate of 73.7% (Andtbacka et al). We hypothesize that combination CVA21 and pembrolizumab will be safe and well-tolerated, and result in improved clinical efficacy through increased expression of PD-L1 following virus therapy.

Trial design: In this phase I trial (NCT02565992), we will enroll 30 patients with advanced melanoma with at least one tumor deposit accessible for injection. The primary endpoint is the safety of CVA21 with pembrolizumab with secondary endpoints of overall response rate, progression-free and overall survival. Correlates include measures of T-cell subsets and antibody responses to melanoma antigens in tumor tissue and peripheral blood. Pre- and post-treatment tumor PD-L1 expression will be assessed and correlated with clinical benefit. Patients will receive up to 4.0 mL of intratumoral CVA21 on days 1, 3, 5, and 8 every 3 weeks for a maximum of 19 total injections, and pembrolizumab 2mg/kg IV every 3 weeks starting on day 8 for up to 2 years. Patients will be evaluated for toxicities until the dose-limiting toxicity (DLT) of CVA21 is reached, and for response by modified WHO criteria. Peripheral blood mononuclear cells will be collected at baseline, prior to pembrolizumab administration, and at study termination, and optional tumor biopsies will be obtained at baseline and at periodic intervals thereafter. The trial is currently screening eligible subjects.

Clinical trial identification: NCT02565992

Legal entity responsible for the study: Viralytics, Limited

Funding: Viralytics, Limited

Disclosure: H.L. Kaufman: Advisory boards for Amgen, EMD Serono, Merck, Prometheus and Sanofi. Speaker’s bureau for Merck but returns all honoraria to Rutgers University. M. Grose, D. Shafren: Employee of Viralytics. All other authors have declared no conflicts of interest.
new diagnostics

1159P
Analytic validation of a clinical circulating tumor DNA assay for patients with solid tumors
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Background: Several circulating tumor DNA (ctDNA) profiling assays are commercially available, and physicians must be empowered to identify assays with the high level of accuracy required to meet the diagnostic needs of their patients. This study describes the analytic validation of a ctDNA assay optimized for clinical care.

Methods: Accuracy and reproducibility were validated using 117 reference samples with known alterations and 268 clinical ctDNA samples. A CLIA-validated NGS assay, droplet digital PCR, and break point PCR were used to validate the alterations identified. A highly optimized, integrated workflow was developed that includes sample collection, storage and transport, ctDNA purification, library generation, and enrichment (solution hybridization capture), followed by high-depth sequencing (HiSeq2500). Computational methods were developed to enable sensitive and specific detection of all alteration classes, including base substitutions, small insertions and deletions (indels), copy number changes, and rearrangements/fusions.

Results: This ctDNA assay demonstrated unprecedented accuracy >99% sensitivity and >99% positive predictive value (PPV) for base substitutions and indels, >99% sensitivity and 98% PPV for rearrangements/fusions with a limit of detection below 0.5%, plus robust detection of high-level, focal amplifications. The assay also accurately reports allele frequency. In 48 clinical ctDNA samples, 85 alterations of all classes were 100% confirmed by orthogonal testing. We also report results comparing alterations from patient-matched ctDNA and FFPE biopsies.

Conclusions: Developing a commercial ctDNA assay requires rigorous analytic validation and the availability of clinically relevant test metrics to ensure reliable interpretation and reporting to optimize targeted treatment options. This rigorous analytic validation study demonstrates high-accuracy detection in blood for all alteration classes, even when mutations are present at low allele frequency, thereby realizing the potential of ctDNA-based molecular profiling for the management of cancer. A large, ongoing prospective clinical trial will provide additional data on the appropriate clinical settings for use of this assay in patient care.

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Foundation Medicine, Inc.

Disclosure: P.J. Stephens, V.A. Miller: Employee of, stockholder in, and holds a leadership position for Foundation Medicine, Inc. T. Clark, M. Kennedy, J. He, G. Young, M. Zhao, M. Coyne, T. Brodie, S. Zhong, M. Bailey, B. Fendler, G. Otto, D. Lipson, J.S. Ross: Employee of and stockholder in Foundation Medicine, Inc. All authors have declared no conflicts of interest.

1160P
Genetic testing by a novel high-purity concentration system for circulating tumor cells independent of epithelial markers
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Background: Genetic analysis of circulating tumor cells (CTCs) is useful as liquid biopsy. However, there are 3 challenging issues in processing of CTC samples for clinical use: [1] numerous normal blood cells in processed samples, [2] loss of CTCs that do not express epithelial markers, and [3] very laborious process. Here, we developed a novel system capable of overcoming all of these problems, which is perfect for the analysis of CTCs.

Methods: Here, we developed a novel system capable of overcoming all of these problems, which is perfect for the analysis of CTCs.

Results: Our CTC analysis system is composed of 5 steps: [1] filtering whole blood followed by immunostaining and magnetic labeling of cells trapped on the filter, [2] depletion of white blood cells (WBCs) in the cells recovered from the filter by magnetic separation, [3] trapping the resultant cells at an observation chamber in a micro-fluidic device using dielectrophoresis, [4] recovering the cells as a concentrated sample after fluorescence microscope observation, and [5] detecting genetic mutation of the cells without nucleic acid purification using the whole sample by quenching probe method. Using whole blood spiked with cultured cancer cell lines (NCI-H2228, NCI-H1650, NCI-H1975, SW620 or MCF-7), we demonstrated our system and detected their genetic mutations (EML4-ALK, EGFR, KRAS or PIK3CA).

Results: Our system successfully detected EML4-ALK, EGFR, KRAS or PIK3CA mutations of the cell lines spiked in 8 mL of whole blood. The detection sensitivity of our method was 1 cell/mL, and the average number of residual nucleated cells was 87 (Table 1). Our system could report the results of genetic mutation detection and each enumeration of cancer cells and residual nucleated cells within 9 hours of starting the processing of whole blood.

Table 1: 1160P Sensitivity and reproducibility results for spiking test

<table>
<thead>
<tr>
<th>test cell line</th>
<th>expected count [cells in 8 mL]</th>
<th>detected count [cells]</th>
<th>residual nucleated cell [cells]</th>
<th>detected EGFR mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI-H1650</td>
<td>8 (SD ± 1)</td>
<td>9 (SD ± 1)</td>
<td>121</td>
<td>ex914del</td>
</tr>
<tr>
<td>NCI-H1975</td>
<td>11 (SD ± 4)</td>
<td>5 (SD ± 4)</td>
<td>80</td>
<td>L858R</td>
</tr>
<tr>
<td>NCI-H1975</td>
<td>7 (SD ± 3)</td>
<td>4 (SD ± 3)</td>
<td>129</td>
<td>L858R</td>
</tr>
<tr>
<td>NCI-H1975</td>
<td>9 (SD ± 3)</td>
<td>7 (SD ± 3)</td>
<td>79</td>
<td>L858R</td>
</tr>
<tr>
<td>NCI-H1975</td>
<td>10 (SD ± 3)</td>
<td>3 (SD ± 3)</td>
<td>91</td>
<td>L858R</td>
</tr>
</tbody>
</table>

Conclusions: Our system would be useful for the analysis of gene mutations in wide-ranging CTC subsets independent of expression of a certain antigen, and may be particularly effective for CTCs that have changed their phenotype.

Legal entity responsible for the study: Arkray, Inc.

Funding: Arkray, Inc.

Disclosure: All authors have declared no conflicts of interest.
patients in many indications. Variant detection frequencies in blood from a representative clinical cohort generally aligned with expected alteration frequencies identified in tissue from published literature.

Clinical trial identification: 42736493ED11001

Legal entity responsible for the study: Janssen Pharmaceutica, University of Washington

Funding: Janssen Pharmaceutica, Resolution Bioscience


Analytical performance of a new liquid biopsy mutation panel for detection of clinically actionable variants


Research and Development, Genomic Health Inc, Redwood City, CA, USA

Background: Assessing alterations in circulating tumor DNA (ctDNA) from liquid biopsies may better reflect tumor heterogeneity, facilitate monitoring of tumor evolution and overcome the challenges of obtaining tissue biopsies. Analytic performance of such assays should be established on a per sample basis, using clinically relevant variants at levels representative of ctDNA. Here we report the analytic performance of a 17-gene panel (OncoType SEQ™, Liquid Select) and illustrate its ability to detect ctDNA in cancer patients.

Methods: Analytical specificity and sensitivity were characterized through determination of Limit of Blank (LoB) and Limit of Detection (LoD) respectively. 73 cell-free DNA (cfDNA) samples from 60 healthy donors were used to determine the LoB and set detection thresholds. A model system using cell line DNA harboring clinically actionable variants was then used to determine the allele fraction (AF)/copy number (CN) required for a 95% rate of detection (LoD), using 30-50ng DNA input. Repeatability and reproducibility was assessed using pools of cfDNA from cancer patients. Finally, liquid biopsies from 15 stage II-IV cancer patients (on or after therapy) were assayed for genomic alterations.

Results: Detection thresholds were set above the LoB corresponding to >99% per sample specificity. LoD was calculated using 105 samples for each variant tested. Mean LoDs were as follows; single nucleotide variants (SNVs), 0.56% AF; insertions/deletions (indels), 0.19% AF; fusions, 0.37% AF, and CN gain, 2.7 copies. Accuracy was verified using additional variant positive and variant negative standards. In the repeatability and reproducibility study using cfDNA pools, on average >95% of expected variants were detected in each run. 10 SNVs and 2 indels were found in the 15 patient plasma samples, ranging from <0.1-3.32% AF.

Conclusions: The 17-gene panel (OncoType SEQ™, Liquid Select) provides high sensitivity, detecting ctDNA at <0.1% in stage III or later disease. In addition, its high specificity and reproducibility ensures reliable patient reporting.

Legal entity responsible for the study: Genomic Health

Funding: Genomic Health

Copy number variant detection by anchored multiplex PCR and next-generation sequencing

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Research and Development, ArcherDX, Inc, Boulder, CO, USA

Background: Copy number variants (CNVs) are common oncogenic drivers, impacting more of the cancer genome than all other types of mutations combined. Next generation sequencing (NGS) of cancer genomes is a highly sensitive method to detecting CNVs for 43 cancer-associated genes. We also developed the Preseq™ DNA QC Assay to determine the integrity of genomic DNA prior to library preparation.

Results: We examined over 150 FFPE tumor samples for genomic DNA integrity and CNV detection using the Preseq™ DNA QC Assay and VariantPlex Solid Tumor kit for NGS. Our data show that NGS-based detection-sensitivity is primarily driven by the integrity of the input genomic DNA, which further predicts the limit of CNV detection. Using optimal input amounts of genomic DNA, the VariantPlex Solid Tumor kit enabled detection of CNVs as low as 2-fold in FFPE samples and in samples with as low as 3% tumor cellularity.

Conclusions: These results demonstrate that AMP-based target enrichment enables sensitive NGS-based detection of low-level CNVs from low-input clinical samples and in samples with low tumor cellularity.

Legal entity responsible for the study: ArcherDX, Inc.

Funding: ArcherDX, Inc.


Comprehensive profiling of thyroid and lung cancers by anchored multiplex PCR and next-generation sequencing

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Background: Thyroid and lung cancer tumorigenesis can be driven by many mutation types occurring across a large set of genes. These include single nucleotide variants (SNVs), insertions and deletions (indels), copy number variants (CNVs) and fusions. As such, a comprehensive assay for multiple classes of genomic aberrations targeting a spectrum of relevant genes has significant implications for the characterization of thyroid and lung tumors. Anchored Multiplex PCR (AMP™) is a target enrichment strategy engineered to preserve the complexity of degraded samples by ligating molecular barcodes with a universal primer binding site for amplification. This enables next generation sequencing (NGS)-based detection of known and novel fusions from RNA, as well as RNA-based variant detection and expression analysis. In addition, high complexity DNA-based libraries allow for high-confidence SNV/indel and CNV detection.

Methods: Sixty two non-small cell lung carcinoma samples were subjected to AMP-based NGS using Archer™ Varibyte and FusionSelect™ libraries with variance in samples with low tumor cellularity.

Results: Our data show that parallel interrogation of DNA and RNA using VariantPlex and FusionPlex CTI assays, respectively, enables simultaneous detection of SNVs, indels, CNVs and fusions from low-input clinical sample types. Furthermore, we show that characterization of gene expression, including detection of splice variants, expression imbalances and whole gene expression levels provides orthogonal verification of detected mutations.

Conclusions: These results demonstrate that AMP-based libraries support simultaneous NGS-based detection of multiple types of genomic aberrations across many genes in lung and thyroid cancer. Furthermore, combined use of RNA- and DNA-based libraries offer cross-validation of findings within a sample.

Legal entity responsible for the study: ArcherDX, Inc.

Funding: ArcherDX, Inc.


Genetic aberrations driving MET deregulation detected with anchored multiplex PCR and next-generation sequencing

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Background: Deregulation of the receptor tyrosine kinase, MET, is associated with aggressive phenotypes in a variety of human cancers, promoting proliferation, invasive growth and angiogenesis. Several types of genetic aberrations can drive MET deregulation, including gene amplification, overexpression, single nucleotide variants (SNVs), exon 14 skipping and fusions. MET is a target of intensive drug development efforts, however the various mutated forms of MET exhibit unique drug sensitivities. Therefore, detection of these mutations has the potential to guide treatments for cancers driven by MET deregulation. Next-generation sequencing (NGS) enables comprehensive detection of all mutation types from whole genomes and transcriptomes. However, low detection sensitivity, high input requirement and high costs render these approaches impractical for routine detection of mutations from low-input clinical sample types. Anchored Multiplex PCR (AMP™) is a target...
enrichment strategy for NGS that, by its scalable and quantitative nature, is well suited for detection of each of the modes deregulation of MET

**Methods:** We developed AMP-based VariantPlex™ and FusionPlex™ library preparation assays for NGS to detect mutations from DNA and RNA, respectively. We designed AMP probes covering the MET gene to detect copy number variants (CNVs) from DNA, and fusions, exon skipping and expression levels from RNA.

**Results:** VariantPlex and FusionPlex kits enabled detection of MET amplifications, confirmed by FISH, and the resulting overexpression in FFPE samples. Exon 14 skipping was also detected and confirmed by RT-qPCR in FFPE and in cells, with concomitant splice site mutations. Lastly, a GTP2/MET gene fusion and a Y1235D activating point mutation were detected.

**Conclusions:** These results show that AMP enables comprehensive and sensitive NGS-based detection of multiple mutation types from low-input clinical sample types.

**Legal entity responsible for the study:** ArcherDX, Inc.

**Funding:** ArcherDX, Inc.


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**1166P**  **Internal tandem duplications in FLT3 detected by anchored multiplex PCR and next-generation sequencing**

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**Background:** Internal tandem duplications (ITDs) in FLT3 are detected in more than 20% of pediatric and adult acute myeloid leukemia (AML) and are associated with a aggressive phenotype. As FLT3-ITD expressed kinases are sensitive to tyrosine kinase inhibitors, there is a considerable interest for the development of novel AML treatments. Capillary gel electrophoresis can detect ITDs but cannot be easily coupled with assays to detect other mutation types common in AML. Next-generation sequencing (NGS)-based methods enable comprehensive detection of multiple mutation types. However, detection of ITDs by NGS is challenging, in part because of their highly variable nature and the difficulties of mapping repeated sequences to a wild-type reference. Anchored Multiplex PCR (AMP™) is a target enrichment strategy for NGS that uses molecular barcoded adaptors and gene-specific primers, permitting open-ended capture of DNA fragments from a single end. We tested whether AMP-based NGS is suitable for FLT3-ITD detection.

**Methods:** We developed the Archer™ VariantPlex Core AML library preparation assay for NGS to detect FLT3-ITDs from genomic DNA extracted from clinical samples. We designed AMP probes to cover the commonly mutated juxtaposed domain and tyrosine kinase domain 1. We further developed a novel de novo sequence assembly algorithm based on over 2000 in silico datasets representing a large range of known ITDs.

**Results:** In silico datasets enabled optimization of the VariantPlex Core AML analysis algorithm, resulting in the detection over 98% of in silico ITDs with no false positives. The VariantPlex Core AML library preparation assay in conjunction with the optimized analysis algorithm enabled sensitive NGS-based detection of ITDs in 16 AML-positive blood samples. These results were consistent with results obtained from standard capillary gel electrophoresis.

**Conclusions:** Our data show that AMP enables accurate NGS-based detection of FLT3-ITDs from clinical DNA samples. As this approach can detect multiple mutation types from a single sample, our VariantPlex Core AML kit enables simultaneous detection of multiple mutations relevant in AML.

**Legal entity responsible for the study:** ArcherDX, Inc.

**Funding:** ArcherDX, Inc.

**Disclosure:** B. van Deusen, M. Bessette, L. Johnson, A. Berlin, M. Banos, L. Griffin, E. Heckman, J. Stahl, A. Licon, B. Kudlow: Full-time employee at ArcherDX, Inc.

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**1167P**  **Functional characterization of variants of unknown significance (VUS) in patients and their responsiveness to targeted therapy drugs (TTD)**

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**Background:** Molecular diagnostics revolutionized cancer care, allowing precision medicine to identify actionable mutations in patients’ tumors. However, VUS are frequently found in potentially actionable genes and lack information for inclusion in treatment strategy. Uncovering the clinical relevance of these variants and their response to TTDs, is a crucial step in the development of precision medicine. To address this, we utilized NovelusDx’s Functional Annotation for Cancer Treatment (FACT) platform, which monitors the activity of signaling pathways by means of a transfected cell-based personalized assay. As a functional platform, FACT reveals activated pathways regardless of the type of mutation, and measures their activity in the presence of TTDs.

**Methods:** We analyzed advanced stage patients, some after multiple lines of treatment, in which a VUS was identified in potentially actionable genes. The patients’ variants were synthesized from the clinically derived NGS data and analyzed with the FACT platform. We compared the activity level induced by the patient’s variants compared to corresponding known hotspots, as well as their response to relevant TTDs.

**Results:** Two Non-small cell lung cancer and one salivary gland patients are presented. VUS mutations were present in the key oncopgenes KRAS, BRAF and EGFR. One patient’s VUS (BRAF N581Y) was functionally inactive by the FACT system compared to the known hot spot mutations, therefore the use of the relevant TTD was predicted to be ineffective. On the other hand, two additional patients’ VUS (KRAS G13P, EGFR S720Y) were found to be active. When measuring the potential benefit of TTDs (Erlotinib, Gefitinib or Trametinib), these active VUS were resistant to off-label treatment at TTDs at levels comparable to the known hotspot mutations providing sound evidence for off-label drug use.

**Conclusions:** The diversity of VUS identified in cancer patients requires a functional assay to segregate clinically relevant variants which may predict response to TTD from those that are clinically inconsequential. The FACT platform can successfully provide sound rationale for considering novel oncogenic mutations as therapeutic, providing new treatment opportunities for these patients.

**Legal entity responsible for the study:** NovelusDx

**Funding:** NovelusDx

**Disclosure:** G. Taric: A full time employee of NovelusDx. Z. Barbash, O. Edelheit, B. Miron, M. Vidne: A full time employee of NovelusDx. All other authors have declared no conflicts of interest.

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**1168P**  **Functional characterization of mutations and their interaction using the novel functional annotation for cancer treatment (FACT) platform**

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**Background:** Mounting evidence indicates that histologically identical cancers are fueled by different sets of driving mutations in each patient. Most tumors possess several genetic alterations capable of driving tumor growth. Targeted therapy drugs (TTD) have demonstrated efficacy by inducing significant tumor regression. A percentage of patients do not respond to TTDs or develop drug resistance due to the interaction of ‘‘cross-talk’’ between multiple alterations providing a bypass mechanism for tumor survival. FACT is capable of functionally quantifying cross-talk driven by multiple mutations, including variants of unknown significance, to improve tailored therapy.

**Methods:** FACT is a cell-based assay which utilizes fluorescent reporters to quantify activity of multiple oncogenic signaling pathways. We focused on canonical resistance mechanisms driven by cross-talk which exact resistance to TTDs. Co-transfection is used to test cross-talk between multiple mutations. Relevant TTDs were tested in FACT to predict patient response to single-drug and combination therapies.

**Results:** FACT quantified activation in a wide range of known oncogenes altered by patients’ mutations in relevant signaling pathways. Using FACT, we were able to demonstrate cross-talk between co-existing mutations in known oncogenes (EGFR + KRAS, ERBB2 + BRAF, etc). These combinations were shown to affect resistance to certain TTDs which could be bypassed with TTD combination therapy.

**Conclusions:** These results demonstrate the value of an assay capable of providing actionable information regarding resistance, fueled by cross-talk, as well as use of combination therapy, in order to select the optimal course of treatment. These interactions, unidentified by NGS, are critical to predicting treatment response and provide another layer of critical information to physicians in the age of precision medicine.

**Legal entity responsible for the study:** N/A

**Funding:** NovelusDx

**Disclosure:** B. Miron, N. Peled, Z. Barbash, O. Edelheit, M. Vidne, R. Sharivkin, G. Taric: NovelusDx.

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**1169P**  **Validation of novel diagnostic kits using the semi-dry dot-blot method for detecting metastatic lymph nodes in breast cancer; distinguishing macrometastases and micrometastases**

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**Background:** The semi-dry dot-blot (SDB) method is a diagnostic procedure for detecting lymph node (LN) metastases. Metastases are confirmed by the presence of...
A novel Tc-99m and fluorescence labeled peptide: Multimodal imaging agent for targeting angiogenesis in a murine tumor model

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Background: The serine-aspartic acid-valine (SDV) peptide binds specifically to integrin αvβ3. In the present study, we successfully developed both Tc-99m and TAMRA labeled TAMRA-GHEG-ECD-SDV peptide to target the angiogenic activity of tumor cells; furthermore, we evaluated the diagnostic performance of TC99m TAMRA-GHEG-ECG-SDV as a dual-modality imaging agent for tumor of the murine model.

Methods: TAMRA-GHEG-ECG-SDV synthesized using Fmoc solid-phase peptide synthesis. Radiolabeling of TAMRA-GHEG-ECG-SDV with Tc-99m was done using ligands exchange methods. Labeling stability and cytotoxicity studies were performed. Gamma camera imaging, biodistribution and ex vivo imaging studies were performed in murine models with HT1080 and HT-29 tumors. Tumor tissue slice was prepared and analyzed using confocal microscopy.

Results: After radiolabeling procedures with Tc-99m, the Tc-99m TAMRA-GHEG-ECG-SDV complexes were prepared in high yield (>99%). Tc-99m TAMRA-GHEG-ECG-SDV was found to be nontoxic to HUVEC and HT-1080 cells at all concentration. On gamma camera imaging study, a substantial uptake of Tc-99m TAMRA-GHEG-ECG-SDV into HT-1080 tumor (integrin αvβ3-positive) and low uptake of Tc-99m TAMRA-GHEG-ECG-SDV into HT-29 tumor (integrin αvβ3-negative) were demonstrated. The HT-1080 tumor-to-normal muscle uptake ratio of Tc-99m TAMRA-GHEG-ECG-SDV reached 6.8 ± 2.3 at 1 h (2.8 ± 0.7, 3.3 ± 1.5 for distinguishing macrometastases from micrometastases was 95.3%, 95.8%, and 95.7%, respectively. Diagnosis was achieved in approximately 20 min using the kits, at a cost of less than 25 US."

Conclusions: The kits in our study were accurate, quick, and cost-effective in diagnosing LN metastases without the loss of LN tissue. The kits ability to distinguish macrometastases from micrometastases was excellent, which is important, clinically.

Legal entity responsible for the study: Ryoa Otsuki

Funding: Nagasaki University Hospital, Department of Surgical Oncology

Disclosure: All authors have declared no conflicts of interest.

A novel Tc-99m and fluorescence labeled peptide: Multimodal imaging agent for targeting angiogenesis in a murine tumor model

Table: 1171P
PD-L1 IHC PD-L1 mRNA T Effectora
n Median b expression 95% CI n Median b expression 95% CI
TC0 and ICS 46 0.99 ± 0.06 0.93 ± 0.06 0.96 ± 0.06
TC1 or ICS 22 0.80 0.46 ± 0.12 0.53 ± 0.16 0.25 ± 0.05
TC1 or ICS 11 1.66 1.56 ± 0.14 1.57 ± 0.16 1.66 ± 0.20
TC3 or ICS 3 1.34 1.29 ± 0.41 1.42 ± 0.49 1.56 ± 0.56

* Includes CD68, CD3, CD4, CD8A, GZMA, GZMB, EOMES, CXCL9, CXCL10, TBX21. b Median expressions are log scale expression (~ACT) relative to the median of TC0 and ICS group. Larger values indicate higher expression.

Legal entity responsible for the study: E. Hoffmann-La Roche, Ltd.

Funding: E. Hoffmann-La Roche, Ltd.


NSCLC multiplex IHC diagnosis of small biopsies

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Background: Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and in 75% of cases is inoperable and diagnosed on small biopsies. The histological subtyping of NSCLC, especially the differentiation between adenocarcinomas (AC) and squamous cell carcinomas (SCC) is important for therapy. Histopathological evaluation of small samples to discriminate between AC and SCC subtypes is often challenging because of poor morphology and insufficient size of the biopsies. Thus, confirmatory immunostainings to support the diagnosis are necessary, while the limited material requires prioritizing the diagnostic and predictive

Methods: We evaluated 139 LNs dissected from 79 breast cancer patients from July 2013 to April 2015 at Nagasaki University Hospital, including 32 dissected axillary LNs and 107 sentinel LNs, sliced at 2 mm intervals and washed with phosphate-buffered saline. The suspended cells in the lavage fluid of sliced LNs were centrifuged and lysed to extract protein. This extracted protein was used with a low-power and a high-power kit to diagnose LN metastasis. The washed LNs were blindly diagnosed by pathologists using hematoxylin and eosin (H&E) stain. Diagnoses based on the kit were compared with their H&E counterpart.

Results: Of the 139 LNs, 55 were assessed as positive and 44 as negative by permanent pathological examination with H&E. Sensitivity, specificity, and accuracy of the low-power kit for detecting LN metastases was 80.7%, 100%, and 92.2%, respectively. In 10 false-negative cases, there were eight micrometastases, producing a sensitivity of 95.3% for detecting macrometastases. Sensitivity, specificity, and accuracy of the high-power kit for detecting LN metastases was 90.9%, 91.7%, and 92.1%, respectively. Combined the low- and high-power kits reached 99.9% for distinguishing macrometastases from micrometastases was 95.3%, 95.8%, and 95.7%, respectively. Diagnosis was achieved in approximately 20 min using the kits, at a cost of less than 25 US.

Conclusions: The kits in our study were accurate, quick, and cost-effective in diagnosing LN metastases without the loss of LN tissue. The kits ability to distinguish macrometastases from micrometastases was excellent, which is important, clinically.

Legal entity responsible for the study: Ryoa Otsuki

Funding: Nagasaki University Hospital, Department of Surgical Oncology

Disclosure: All authors have declared no conflicts of interest.

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biomarkers to be tested. Multiple immunostainings in NSCLC help discriminating AC from SCC including cytokeratin 5 and 7 (CK5 and CK7) and the transcriptional factors TTF1 and P4, and in addition ALK-staining is required for selecting patients to targeted therapy. To avoid prioritizing the biomarkers and save tissue for molecular testing we have developed a multiplexing immunohistochemical diagnostic analysis that allows the detection of the 5 biomarkers on a single tissue section established, clinically used primary antibodies.

Methods: Surgical samples and needle biopsies from NSCLC patients of AC and SCC subtypes were obtained from Rigshospitalet. Unmodified primary antibodies for the detection of CK5, CK7, TTF1, P40 and ALK were used.

Results: Multiplex immunohistochemical staining of tissue sections with primary antibodies of the same origin and isotype required designing a sequential assay format that allows each biomarker assay to be performed individually by following the result and subsequently ‘deleting’ the signal before moving on with the next biomarker assay. We show that this can be done on one single tissue section, by providing evidence of the efficiency of deleting antibodies in between assays, and the ability to combine and superimpose individual images of biomarker assays at the end of the sequential analysis.

Conclusions: We have developed a immunofluorescent diagnostic assay that can detect up to five different biomarkers relevant for NSCLC-diagnostic applicable to both surgical and biotic samples. The assay format is independent of the origin and isotype of primary antibodies.

Legal entity responsible for the study: Bioneer

Funding: Bioneer

Disclosure: All authors have declared no conflicts of interest.

Detection of NRAS, KRAS and BRAF mutations in FFPE derived DNA with a novel targeted resequencing-based diagnostics assay


Background: Identification of cancer-associated mutations has become standard care for cancer treatment. Somatic mutations in NRAS, KRAS and BRAF genes are important to decide the treatment options for patients with cancer. Mutations in NRAS, KRAS or BRAF help to determine the treatment options for patients when EGFR inhibitor or BRAF inhibitor treatment is considered. The novel SOMATIC 1 MASTRTM Plus Dx® assay has been developed to allow analysis of the hotspot mutations or of the full coding region of KRAS, NRAS and BRAF genes in combination with Next Generation Sequencing (NGS).

Methods: To assess the performance characteristics of the SOMATIC 1 MASTRTM Plus Dx® assay, a multicenter study was performed. The performance of SOMATIC 1 MASTRTM Plus Dx to detect single nucleotide variants (SNV) and small insertions and deletions (indels) in the KRAS, NRAS and BRAF genes at a variant allele frequency (VAF) of 5% in the entire coding region and for specific hotspot mutations was evaluated. The sample population comprised 252 formalin-fixed, paraffin-embedded (FFPE) clinical samples derived from a variety of different cancer types and proficiency samples (Tru-Q Reference Standards, Horizon Discovery). Amplicon libraries were analysed using Illumina MiSeq platform. Data analysis was performed with the SeqNext software (Illumina Medical Systems) and the Sophia DDM platform (IllumIRIS, somatic1_v2).

Results: SOMATIC 1 MASTRTM Plus Dx® showed amplification uniformity of 97.8% (% of amplicons covered at 0.2x of the mean coverage) and a target specificity of 99.1%. The overall limit of detection (LOD) of the assay was determined as 2% VAF, and showed to be as low as 1% for hotspot mutations. Diagnostically, the assay showed 99.96% (95% CI ≥ 99.90% ) accuracy, 99.96% (95% CI ≥ 99.90%) specificity and 100% (95% CI ≥ 98.54 %) sensitivity. Furthermore, SOMATIC 1 MASTRTM Plus Dx® assay showed to be 99.99% (95% CI ≥ 99.97 %) repeatable and 99.96% (95% CI ≥ 99.91%) reproducible.

Conclusions: We have established a targeted and cost-effective NGS assay for the detection of KRAS, NRAS, and BRAF somatic mutations in clinical FFPE samples that can be routinely incorporated into clinical practice.

Legal entity responsible for the study: Biocartis

Funding: Multiplicom

Disclosure: All authors have declared no conflicts of interest.

Ultra-rapid, sensitive, and fully automated extended RAS testing for metastatic colorectal cancer – evaluation of an NRAS/BRAF/EGFR492 module

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Biocartis, Mechelen, Belgium, 2Multiplicom, Niel, Belgium

Background: Extended RAS testing in codons 12, 13, 59, 61, 117, and 146 in exons 2, 3, and 4 of the KRAS and NRAS genes is now mandatory before anti-EGFR therapy in metastatic colorectal cancer (mCRC) patients. BRAF and EGFR c65ommunutation status have been shown to play a crucial role in predicting non-responsiveness in mCRC patients receiving anti-EGFR therapy. Current methods for testing of extended RAS, BRAF and the new EGFR c6ommutations are laborious and often require ≥ 5 working days.

Methods: The Idylla platform (Biocartis, Mechelen, Belgium) is a CE marked, fully automated sample-to-result, real-time PCR molecular diagnostics system. The Idylla NRAS-BRAF-EGFR492 module is an assay for formalin-fixed paraffin-embedded (FFPE) tissue samples from mCRC patients for the analysis of 18 NRAS (codons 12, 13, 59, 61, 117, and 146 in exons 2, 3, and 4), 2 BRAF (codon 600), and 2 EGFR (codon 492) mutations. The Idylla NRAS-BRAF-EGFR492 Mutation Assay was compared with routine sequencing technologies at five centers (BioPath Innovations, Copenhagen University Hospital, Copenhagen, Denmark, 2Anatomic Pathology Laboratory, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium, 3Pathology Department, University Hospital of the Mar, Barcelona, Spain, 4Medical Oncology, University Hospital of the Mar, Barcelona, Spain).

Results: Positive predicative agreement was 97.2% (n = 106), 100% (n = 100) and 100% (n = 1) and negative predicative agreement was 99.9% (n = 348), 99.9% (n = 412) and 100% (n = 444) for NRAS, BRAF and EGFR, respectively. One BRAF V600E sample detected by Idylla only was confirmed with digital droplet PCR. No cross-reactivity was observed in KRAS positive samples indicating the high specificity of the assay towards NRAS mutations. Fourteen mutations showed an LOD of ≤ 10%, 10 mutations of ≤ 5% and one mutation showed an LOD of 0%.

Conclusions: Given its high sensitivity and specificity, the Idylla NRAS-BRAF-EGFR492 Mutation Assay is ideally suited for rapid detection of NRAS, BRAF and EGFR mutations. Together with the Idylla KRAS Mutation Test (CE-IVD), sample-to-result extended RAS testing on 39 mutations can now be performed in only 2 hours.

Legal entity responsible for the study: Biocartis

Funding: Biocartis

Disclosure: All authors have declared no conflicts of interest.
Hybrid-capture based sequencing assays to detect novel alterations in BRAF from tissue and liquid biopsies

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Background: In recent years advances in translational research have led to the characterization of oncogenic drivers and to the development of their respective targeted inhibitors. Melanomas harbouring the activating BRAF V600E mutation, for example, exhibit high sensitivity towards site-directed inhibitors, translating into a beneficial clinical response. In contrast to standard PCR or FISH- based diagnostics, limited to detect specific, well-established mutations or translocations, NEO is a comprehensive molecular diagnostics platform, capable of detecting genomic alterations including point mutations, small insertions and deletions (Indels), copy number alterations and translocations from both, liquid biopsy (NEOliquid) and tumor tissue (NEOplus) samples.

Methods: NEO New Oncology is able to detect clinically relevant genomic alterations from clinical specimen with high sensitivity and specificity using a hybrid-capture based NGS technology. NEOliquid is specifically designed for detection genomic alterations from cell-free DNA of liquid biopsies and covers a panel of more than 30 cancer-related genes. NEOplus is applied to FFPE tumor tissue and can detect somatic alterations in more than 90 clinically relevant cancer genes.

Results: Using the NEO platform we were able to detect previously unidentified alterations in BRAF from tissue specimen and liquid biopsies, which would have remained undetected by current routine diagnostics. A likely activating in-frame kinase-domain deletion was detected in a liquid biopsy from a kidney cancer, a tumor entity not commonly linked to alterations in BRAF. Additionally, we detected novel genomic rearrangements involving the BRAF gene locus in a lung cancer and strikingly in a pre-diagnosed BRAF(V600E)-negative melanoma sample. Patients harbouiring these atypical BRAF alterations might potentially benefit from treatment with pan-BRAF or MEK inhibitors.

Conclusions: In addition to the reliable and comprehensive detection of known hot-spot alterations routinely tested in cancer diagnostics, the NEO platform is efficient in detecting novel and potentially targetable alterations even in already established, well-defined oncogenes.

Legal entity responsible for the study: NEO New Oncology

Disclosure: J. Crown: member of the aboard of NEO New Oncology. All other authors have declared no conflicts of interest.
NSCLC, early stage

11780 Multi-centre randomized controlled study comparing adjuvant vs neo-adjuvant chemotherapy with docetaxel plus carboplatin in resectable stage IB to IIIA NSCLC: final results of CSLCG0501

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Background: Adjuvant chemotherapy is recommended for completely resected stage II-IIIA NSCLC. Indirect comparison meta-analysis of adjuvant vs neoadjuvant therapy showed no difference in survival. This study was conducted to compare DFS between adjuvant chemotherapy and neoadjuvant chemotherapy among patients with resectable NSCLC.

Methods: Patients with stage IB-IIA NSCLC were eligible. They were randomly assigned to 3 cycles adjuvant DC (Docetaxel: 75mg/m2, Carboplatin: AUC = 5 on day 1 every 4 weeks) or 3 cycles neoadjuvant DC at the same schedule followed by surgery 3-6 wk after chemotherapy. The primary end point was 3 years Disease Free Survival (DFS); secondary end points were 3yrs and 5yrs Overall Survival (OS) and Safety. Planned sample size is 410. The trial was closed early due to slow accrual.

Results: Between March 2006 and May 2011, 214 patients were randomized from 13 institutes, among them 198 patients were randomized. 97 were assigned to neoadjuvant (N) arm and 101 to the adjuvant (A) arm. The median age was 58, male accounted for 80.3%, adenocarcinoma 48.5%, stage Ib, II a, II b and IIIa were 32.5%, 12.2%, 28.4% and 26.9%, respectively. Two arms were balanced. 100% cases received neoadjuvant chemo and 87.4% finished the planned adjuvant chemotherapy. No unexpected toxicities were seen and 41.2% of patients experienced grade 3-4 neutropenia. One toxicity-related death occurred in the A arm. One patient died of peripertative pulmonary embolism in N arm. The ORR was 34% and 14% patients developed PD in N arm. The 3yrs DFS was 56.0% (A) vs 43.0% (N) with HR 0.66, 95%CI 0.44-1.00, P = 0.049. The 3yrs OS was 50.0% (A) vs 33.0% (N), HR0.69, 95%CI 0.48-1.00, P = 0.051, 5yrs OS was 60.0% (A) vs 43.0% (N), HR0.66, 95%CI 0.44-1.00, P = 0.049.

Conclusions: Adjuvant chemotherapy or neoadjuvant with docetaxel plus carboplatin in resectable clinical stage IB-IIIA NSCLC are feasible and safe. The final results showed no difference in 3yrs DFS and OS between two arms. 5yrs DFS in arm A was superior to arm N.

Clinical trial identification: NCT00321334

Legal entity responsible for the study: N/A

Funding: Chinese Society of Lung Cancer

Disclosure: Y-L. Wu: Speaker fees from Roche, AstraZeneca, Eli Lilly, Pfizer and Chinese Society of Lung Cancer

Legal entity responsible for the study: University Hospital of Udine

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

11781 Elevated fraction of CTLA-4(+) and PD-1(+) T cells in peripheral blood with stimulation of Th1, Th2 and Th17 type immune response after stereotactic radiotherapy for early lung cancer – a prospective study

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Background: Stereotactic ablative radiotherapy (SABR) has been successfully used in patients with medically inoperable non-small cell lung cancer (NSCLC). High physical doses of radiotherapy translate into extremely high biological doses more effective in tumor control. Other mechanisms including immune are also postulated. The aim of our study was to prospectively assess the effect of high dose ionizing radiation of the lung tumor on changes in the expression of peripheral T cell activation markers (AM) - CTLA-4, PD-1 and transcription factors (TF) associated with Th1, Th2, Th17 and Th1 type of CD4+ T cells (T-bet, GATA-3, ROR-yt positive, respectively), and a reduction of T-reg - Fox-P3 (+) fraction.

Methods: In patients with previously untreated NSCLC in stage T1-2aN0M0 receiving SABR peripheral blood mononuclear cells (PBMC) and blood serum was drawn three times - before 1 fraction (D1), two weeks (D2) and 3 months (D3) after radiotherapy. Expression level of selected AM, TF and cytokines was measured by flow cytometry.

Results: From September 2013 to March 2016 we enrolled 94 patients aged 53 to 87 years (median 74 years). All patients underwent SABR in accordance with local standards. The D1, D2 and D3 control points were achieved by 92, 92 and 78 patients, respectively. A significant increase in the fraction of CD4+ and CD8+ T-cells with expression of PD-1 and CTLA-4 AM was found in all patients at D2 and D3 control points. Additionally increased level of Th1, Th2 and Th17 type of CD4+ T-cells (T-bet, GATA-3, ROR-yt positive, respectively), and a reduction of T-reg - Fox-P3 (+) fraction with simultaneous elevation of Th1 (IFN-Y), Th2 (IL-4, IL-13) and Th17 (IL17) cytokines was also detected at D2 and D3 control points.

Conclusions: In patients with early NSCLC, enhanced expression of AM after SABR suggests the activation of CD4+ and CD8+ T-cells. These changes correlate with stimulation of Th1, Th2 and Th17 type systemic immune response and reduction of the number of T-reg cells. The project was financed by the Polish National Science Centre, Grant no UMO-2012/07/B/NZ5/00587.

Legal entity responsible for the study: Medical University of Gdańsk

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Disclosure: R. Zaucha: Travel grants from Amgen, Roche, MSD, BMS. Educational grants from Roche, MSD, Nurixia. All above were not connected to presented research. All other authors have declared no conflicts of interest.

11784 Low dose CT scan screening versus empiric surveillance in asbestos exposed subjects: Update of ATOM 002 study

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Background: Low dose CT scan screening (LDCT) has been proven effective in detecting early-stage lung cancer in asbestos exposed workers, but there is no evidence based indication concerning the follow up of these subjects. Aim of this study is to evaluate whether LDCT screening, compared with empiric health surveillance program, could be effective in reducing mortality for lung cancer and/or malignant pleural mesothelioma in asbestos-exposed former workers.

Methods: The ATOM002 prospective non-randomized study enrolled a cohort of 2433 occupationally asbestos-exposed men. The prognostic role of LDCT was investigated through Cox regression in terms of survival for all causes, all cancers, lung cancer and pleural mesothelioma. Multivariate models were adjusted for smoking habits, age at start of follow-up, level of exposure to asbestos and Charleston-Quan comorbidity index. External comparison was possible by estimating the standardized mortality rate ratio (SMR) using Israeli Venetia Giulia regional standard rates (SMR_FVG) and Italian standard rates (SMR_ITA).

Results: Among the total population, 926 men were allocated to the LDCT cohort (ATOM002-P) and 1307 to standard follow-up (ATOM002-NP). Lung cancer crude mortality was 99.4 per 100,000 person-year in ATOM002-P (Obs = 4) compared to 430.4 per 100,000 person-year in ATOM002-NP (Obs = 50). Multivariate analysis highlighted a significant mortality reduction in the ATOM002-P cohort (HR = 0.41 IC95% 0.17-0.96). Even though it was not significant, pleural mesothelioma mortality were not significantly affected (HR = 0.97 IC95% 0.62-1.50; HR = 0.86 IC95% 0.31-2.41, respectively). Notably, a reduction in mortality of the ATOM002-P cohort was also observed in respect to the general population (SMR_FVG = 0.55 IC95% 0.24-1.09, SMR_ITA = 0.51 IC95% 0.22-1.01).

Conclusions: In our study we found a reduction in the risk of death from lung cancer, compared with national figures but no reduction in risk of death from pleural mesothelioma. These data could reasonably be considered within public surveillance programs for selected, high risk, population.

Legal entity responsible for the study: University Hospital of Udine

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
Clinicopathological analysis of programmed death-ligand 1 (PD-L1) expression on tumor cells (TC) and tumor-infiltrating immune cells (IC) in surgically resected non-small cell lung cancer (NSCLC) patients (pts)

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Background: Advanced NSCLC with PD-L1 expression on TC and IC has shown higher sensitivity to the PD-L1 inhibitor atezolizumab. This study is to examine the association between PD-L1 expression on TC and IC and clinicopathological characteristics, IGF/PALK driver oncogenes status and prognosis in surgically resected NSCLC.

Methods: We analyzed 514 NSCLC pts who underwent surgical resection from November 2005 to March 2011 at the National Cancer Center Hospital East. The PD-L1 expression on TC (4 levels of expression: TC0-3) and IC (IC0-3) was evaluated using the Ventana PD-L1 (SP263) antibody IHC assay as recently described (Lancet 2016; 387: 1837-46). TC1-3 and IC1-3 were defined as positive, respectively.

Results: Median age at tumor resection was 68 (range 30-93) years, male/female 63/37%; smoker/non-smoker 69/31%; squamous cell carcinoma (Sq) non-Sq 13/87%; IGF/PALK mutations (mut) +/- 36/64%; ALK fusion +/- 3/97%; p-stage U/I/III/IV 19/19/19/2%. PD-L1 expression was as follows; TC1/2/3: 81/79/9%, IC1/2/3: 38/34/22/6%. PD-L1 expression on TC was observed in 19% of tumors, and on IC in 62% of specimens. PD-L1 expression on TC or IC (i.e. TC1-3 or IC1-3) was observed in 63%. Smoking and p-stage II-IV were associated with PD-L1 expression on both TC and IC (P < 0.05), while EGFR mut (-) and Sq were characterized by higher expression on TC and IC, respectively (P < 0.05). Overall survival (OS) in NSCLC pts with PD-L1 expression on both TC and IC (P < 0.05), and OS in pts with PD-L1 expression on IC (P < 0.05) was observed in 63%.

Conclusions: Smoking and advanced p-stage were associated with PD-L1 expression on both TC and IC, while Sq was associated with PD-L1 expression on IC and EGFR mut (-) on TC. PD-L1 expression on TC and IC was not independent prognostic factor.

Legal entity responsible for the study: National Cancer Center Hospital East
Funding: Chugai Pharmaceutical Co., Ltd.

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RICTOR/P38K/mTOR as a clinically relevant driver of poor prognosis in squamous cell lung carcinoma (SqCLC): Preliminary results of prognostic outliers according to a validated clinicopathological model

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Background: We previously validated a clinical risk classification model for resected SqCLC by combining clinicopathological predictors to discriminate patients’ (pts) prognosis (Pilotto TO 2015). Here we investigate the molecular portrait of prognostic outliers to identify differentially expressed, potentially druggable molecular targets (AIRC/MFAG project no. 14282).

Methods: On the basis of the published 3-class model, 176 and 46 pts with good and poor prognosis, respectively, were identified. Next Generation Sequencing (NGS) analysis (Ion Proton system, Ion Ampliseq custom panel) evaluating Somatic Mutations (SM) and Copy Number Alterations (CNA) of 44 genes was performed; RNA expression, immunohistochemistry (IHC), immuno-fluorescence (IF) were performed on Tissue Micro-Arrays (TMA). Descriptive statistics was adopted; continuous variables were dichotomized according to AUC or medians.

Results: The distribution of relevant SM and CNA analysis of 66 pts according to prognosis (good: 27, poor: 39) is reported in the table.

Table: 1182P

<table>
<thead>
<tr>
<th>Analysis (NGS)</th>
<th>Gene</th>
<th>Good: 27 pts [%]</th>
<th>Poor: 33 pts [%]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM</td>
<td>PI3KCA</td>
<td>3 [9.1]</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>NOTCH1</td>
<td>2 [7.4]</td>
<td>0</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>CUL3</td>
<td>2 [7.4]</td>
<td>0</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>DDR2</td>
<td>4 [11.1]</td>
<td>0</td>
<td>0.085</td>
</tr>
<tr>
<td></td>
<td>CDH10</td>
<td>14 [4.8]</td>
<td>1 [3.0]</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>CDH1</td>
<td>11 [3.0]</td>
<td>1 [3.0]</td>
<td>0.3</td>
</tr>
<tr>
<td>CNA Gains</td>
<td>RICTOR</td>
<td>1 [3.7]</td>
<td>9 [27.3]</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>SOX2</td>
<td>20 [74.1]</td>
<td>17 [51.5]</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>CANK23</td>
<td>6 [22.2]</td>
<td>1 [3.0]</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>PTEF1</td>
<td>11 [40.7]</td>
<td>17 [51.5]</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>RBI</td>
<td>8 [29.6]</td>
<td>17 [51.5]</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>SMAD4</td>
<td>9 [33.3]</td>
<td>19 [57.6]</td>
<td>0.074</td>
</tr>
</tbody>
</table>

No significant differences in terms of phospho-mTOR and PD-L1 IHC expression were found in the 2 different prognostic subgroups. Patients with concurrent high PD1, SNAI and Vimentin RNA expression were significantly more likely to be at poor prognosis (p = 0.003).

Conclusions: Although performed on a limited number of pts, the approach to comprehensively analyze DNA, RNA and proteins, using different methodologies, strengthens the clinically relevance of RICTOR/P38K/mTOR signaling cascade activation in determining the poor prognosis of SqCLC. The possibility to inhibit this pathway with selective agents is currently under investigation in vivo in preclinical models.

Legal entity responsible for the study: University of Verona, Verona, Italy
Funding: Associazione Italiana per la Ricerca sul Cancro (AIRC) MFAG Project 14282.

Disclosure: All authors have declared no conflicts of interest.

Assessment of efficacy of adjuvant chemotherapy for non-small cell lung cancer with metastatic ability involving ACTN4

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Background: Selection of patients with high metastatic ability of non-small cell lung cancer (NSCLC) has the potential to predict the clinical benefit of adjuvant chemotherapy (ADC). ACTN4 is an oncogene associated with cancer metastasis. To
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demonstrate the clinical utility of a predictive biomarker for the efficacy of ADC for NSCLC, we analyzed clinical and preclinical data.

Methods: In Step 1, we reanalyzed the impact of ACTN4 on the efficacy of ADC from clinical information and mRNA profiles from the public database of a randomized phase III trial of adjuvant vinorelbine plus cisplatin after complete resection of stage IB or III NSCLC (JBR.10), which was a clinical trial probing the clinical benefits of ADC in stage IB/II patients with NSCLC. In Step 2, we measured ACTN4 protein levels in patients with completely resected stage II or IIIA lung adenocarcinoma at the National Cancer Center Hospital (NCCH) from 2008 to 2011 using immunohistochemistry (IHC). We then retrospectively compared survival between ADC treated with platinum doublet and observation (OBS) groups. In Step 3, we investigated the biological functions of ACTN4 with the A549 lung adenocarcinoma cell line, which has gene amplification of ACTN4.

Results: In Step 1, the 133 patients enrolled in JBR.10 were divided into two groups by expression of the ACTN4 transcript: an ACTN4-positive (ACTN4+) group (n = 23) and an ACTN4-negative (ACTN4−) group (n = 108). In the ACTN4+ group, overall survival (OS) was significantly longer in ADC subjects (n = 15) compared with OBS (n = 10) (hazard ratio [HR] = 0.27, p = 0.042). However, no differences in OS were noted between ADC (n = 56) and OBS (n = 52) subjects in the ACTN4− group. In Step 2, 1,488 eligible patients were classified into two groups based on IHC findings. In the ACTN4-HIC− group (n = 77), mean survival was longer in the ADC patients (n = 23) than in OBS patients (n = 53) (HR = 0.507, p = 0.028). In contrast, the ACTN4-HIC+ group (n = 73) showed no tangible survival benefit with ADC. In Step 3, the metastatic potential of A549 was significantly reduced by ACTN4 shRNA. Clinical data and biological assays suggested ACTN4 as a potential predictive biomarker for the efficacy of ADC in patients with NSCLC.

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Funding: AMED

Disclosure: All authors have declared no conflicts of interest.

Are the criteria indicating patients to be “medically inoperable” that are used in clinical trials on stereotactic body radiotherapy appropriate for patients with early stage non-small cell lung cancer?

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Background: The standard treatment for patients with early stage non-small cell lung cancer (NSCLC) is surgical resection. Stereotactic body radiotherapy (SBRT) has recently been investigated as an alternative treatment in clinical trials, especially for medically inoperable (MI) patients. However, no clear rationale for the criteria used to determine whether or not a patient is MI has yet been demonstrated.

Methods: Between January 2004 and October 2012, 740 patients underwent surgical resection for clinical stage IA NSCLC. In the present study, MI was defined as patients with FEV1 ≤ 80% predicted, NSCLC ≤ 40%, PaO2 ≤ 70mmHg, PaCO2 ≥ 50mmHg, or three or more severe comorbidities, based on the criteria of MI that are frequently used in clinical trials in SBRT for NSCLC patients. The clinicopathological characteristics and surgical outcomes were compared between the MI patients (n = 91) and operable patients (n = 649).

Results: The proportion of males, elderly, smokers and those with a non-adenocarcinoma histology were higher in MI patients than in operable patients. No statistical differences were observed in the proportion of pathological stage IA between the groups (P = 0.09). Limited operation (wedge lung resection or segmentectomy) was performed for 37 (41%) MI and 227 (35%) operable patients (P = 0.3). The rates of overall morbidity (39% vs 23%, P = 0.002) and 90-day mortality (3% vs 0.5%, P = 0.038) were higher in the MI patients than those in the operable patients. Although overall survival was significantly worse in the MI patients (P = 0.004), there were no significant differences in cancer-specific survival between the two groups (P = 0.5).

Conclusions: Surgical resection can be performed safely in the MI patients with an equivalent cancer-specific survival to that observed in the operable patients. The overall survival was superior to that noted in previously reported clinical trials of SBRT in MI patients with early stage NSCLC. Therefore, the current criteria of MI used in clinical trials of SBRT in NSCLC patients are not appropriate for evaluating the true degree of operability.

Legal entity responsible for the study: The institutional review board of Juntendo University School of Medicine

Funding: A Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan

Disclosure: All authors have declared no conflicts of interest.

Prognostic role of texture analysis in lung cancer treated with stereotactic ablative radiotherapy (SABR)

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Background: Stereotactic ablative radiotherapy (SABR) is widely used in lung cancer primary treatment. The aim of present study is to evaluate the texture analysis as a predictive factor of treatment response.

Methods: This single center retrospective study included fifty-six consecutive patients (January 2011 – December 2014) with early stage lung cancer (T1-2a, N0) treated with SABR. The diagnostic CT DCM images pre- and post- SABR were collected and analysed with an automated (message) macro and typical texture analysis parameters were evaluated: mean (m), standard deviation (sd), skewness (sk), kurtosis (k), entropy (e) and uniformity (u). We analyzed progression free survival with sampling of lung progression (PFS-in-field and PFS-out-field) after treatment and overall survival (OS), calculated with Kaplan-Meier method.

Results: During the observation period 15 patients (26.8%) showed evidence of recurrence, divided in recurrence “in field” in 5 patients (16.1%) and “out of field” recurrence in 11 patients (19.6%). Five patients developed both “in field” and “out of field” recurrence; 14 patients (23%) died. Pre SABR parameters Entropy (e) and uniformity (u) were significantly associated with PFS “in field” (p<0,031), whereas kurtosis (k) was significantly associated with PFS “out of field” (p<0,031). Mean (m) was significantly associated with OS (p<0,001). Post SABR parameters entropy (e) was associated with PFS “in field” (p<0,009), whereas mean (m) was associated with PFS “out of field” (p<0,001). A rise in mean (p<0,01), entropy (p<0,028) and a decrease in uniformity (p<0,028) resulted to be significantly associated with PFS “out of field”.

Conclusions: Our results appear to be very promising since the knowledge of the predictive factors of SABR could drive the selection of the best treatment in these patients (i.e. dose increasing in the patients at higher risk? Concurrent chemoradiation? Intensified follow up?). Further studies on large patient series are needed to best estimate the present preliminary data.

Legal entity responsible for the study: Unit of Radiation Oncology, University Hospital of Siena

Funding: Unit of Radiation Oncology, University Hospital of Siena

Disclosure: All authors have declared no conflicts of interest.

Good news for French NSCLC patients: Distance between chest and surgical departments did not impair outcome

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Background: Surgery remains a major treatment option in lung cancer in particular at early stages. Recent Australian and UK studies have shown that patients with NSCLC were less likely to have surgery and more likely to die if they were first seen at a non-specialized surgical centre, or with increasing distance to the nearest specialist hospital. In France, not all general hospitals have a thoracic surgery department. We assessed the impact on patient outcome of the distance between the chest and thoracic surgery Departments.

Methods: KBP-2010-CPHG is a prospective multicentre epidemiological study promoted by the French College of General Hospital Respiratory Physicians (CPHG), including 7,051 patients followed for primary lung cancer diagnosed in 2010 in the chest department of 104 general hospitals. The distance from the usual thoracic surgery department in 2010 was collected for each chest department in 2015. Univariate and multivariate analyses were performed to identify independent factors for surgery and mortality. Distance was included in the model as a 4-class variable: 0 (same hospital), 1-34, 35-79, and ≥ 80 km. 6,083 patients had a NSCLC; 1,185P

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1157 (19%) were operated on. Independent factors for surgery were: young age, early disease, good performance status, and cancer histological type. Distance was not an independent factor for surgery: OR [95% CI] was 0.971 [0.74-1.274] (p = 0.833), 0.883 [0.662-1.178] (p = 0.399), and 1.015 [0.783-1.317] (p = 0.91) for 1-34, 35-79, and ≥ 80 km vs. 0 km. 1,939 patients had stage I to IIIA NSCLC; 1070 (55%) were operated on. Independent risk factors for mortality were old age, male gender, advanced disease, and poor performance status. Distance was not an independent risk factor for mortality: OR [95% CI] was 1.016 [0.83-1.244] (p = 0.878), 1.089 [0.882-1.344] (p = 0.427), and 1.011 [0.829-1.233] (p = 0.915) for 1-34, 35-79, and ≥ 80 km vs. 0 km.

Conclusions: In France, in 2010, the absence of an on-site thoracic surgery department did not impair outcome in NSCLC patients managed in the chest department of general hospitals.

Legal entity responsible for the study: Collège des Pneumologues des Hopitaux Généraux (CPHG)

Funding: KBP-2010-CPHG is a study promoted by the CPHG with the help of the endowment fund Recherche en Santé Respiratoire of the CNMR and Pneumologie development, and funded by the following laboratories: AstraZeneca, BMS, Boehringer Ingelheim, Chugai, GlaxoSmithKline, Lilly France, Pierre Fabre Oncologie, Pfizer, Roche, and Sanofi-Aventis.

Disclosure: All authors have declared no conflicts of interest.
Multigene expression profile for predicting efficacy of cisplatin and vinorelbine in non-small cell lung cancer


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Background: There is a need for biomarkers to predict efficay of adjuvant chemotherapy in resected non-small cell lung cancer (NSCLC). Presented is a combined cisplatin and vinorelbine marker from a previously validated model system [1] tested in two cohorts.

Methods: The profiles consist of correlated in vitro cytotoxicity of cisplatin and vinorelbine and mRNA expressions. Then each profile is correlated to mRNA expression of 3500 tumors. The cohorts are 1) a publicly available dataset with 133 completely resected stage II-II NSCLC patients, 71 of whom received adjuvant cisplatin and vinorelbine (ACT) and 62 patients who had no adjuvant treatment (OBS) [2] and 2) 95 stage Ib-IIb completely resected NSCLC patients who all received adjuvant cisplatin and vinorelbine [3]. Endpoint is cancer specific survival.

Results: The combined cisplatin and vinorelbine scores resulted in a continuous covariate showed 1) a Hazard Ratio (HR) of 0.265 (95% CI 0.079-0.889), p = 0.032 in the ACT cohort (sensitive versus resistant), and no significant discrimination in the OBS cohort (HR = 1.28 (95% CI 0.46-3.835), p = 0.60). A multivariate model adjusted for stage demonstrated significance for ACT (HR = 0.284 (95% CI 0.086-0.944), p = 0.040) but not for OBS (HR = 1.702 (95% CI 0.575-5.036), p = 0.34). The combined profiles resulted in 2) a significant prediction for up to 3 years from surgery (HR = 0.143 (95% CI 0.038-0.542), p = 0.004, scored as a continuous covariate). A multivariate model adjusted for stage showed that the predictor remained significant (HR = 0.275 (95% CI 0.080-0.930, 0.512), p = 0.004). A pooled analysis of the two treated cohorts resulted in a significant prediction (HR = 0.187, 95% CI 0.069-0.508, p = 0.001) up to 3 years from surgery using a random effects model.


Clinical trial identification: Danish Trial Protocol Number H-B-2007-099

Legal entity responsible for the study: Medical Prognosis Institute, Hoersholm, Denmark Dept. of Oncology, Rigshospitalet, Copenhagen, Denmark

Funding: Medical Prognosis Institute, biotech company Markedsmodningsfonden Kraftef iKampempee


doi:10.1093/annonc/mdv382
Functional profiling of oncogenic mutations in lung cancer patients (NCT02274025) - interim results

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Background: Epidermal growth factor receptor (EGFR) inhibitors have shown efficacy in treating EGFR-mutation positive (EGFR+) non-small cell lung cancer (NSCLC). However, selecting EGFR inhibitors is challenging due to differential responses between pts and resistance mutations. We profiled EGFR mutations and their response to EGFR inhibitors using the Functional Annotation for Cancer Treatment (FACT) platform, which characterizes mutations by monitoring the activity of signaling pathways, via a transfected cell-based assay. As a functional platform, FACT reveals activation regardless of prior knowledge of a specific mutation.

Methods: The study included pts with suspected lung cancer undergoing biopsy/ resection. EGFR mutational status was verified by NGS. Using the FACT platform, we analyzed the oncogenic signaling activity of EGFR mutations in these pts and response to physician chosen EGFR inhibitors compared to observed clinical responses assessed by cross-sectional imaging.

Results: Of 23 pts enrolled thus far, 4 pts were EGFR+ and 3 were treated with EGFR inhibitors (erlotinib, gefitinib, afatinib, AZD9291). The first pt had a complex EGFR mutation (T790M/I716T/L858R) and initially responded to erlotinib and after metastatic PD was treated with afatinib. The second pt had two alterations (exon 19 deletion/T790M) failed gefitinib and switched to AZD9291 with good response. The third pt had a common (L858R) mutation treated with erlotinib with good response. In all three pts, FACT assessed oncogenic signaling of the mutations and predicted responsiveness to EGFR inhibitors in accordance with observed clinical outcomes.

Conclusions: This study highlights the utility of functionally profiling mutations, specifically in cases where multiple treatment options are available. We demonstrate that measured signaling activity of the EGFR mutations tested and sensitivity to different targeted therapies was correlated with clinical outcomes in these pts. Clinical trial identification: NCT02274025

Legal entity responsible for the study: N/A

Funding: NovellusDx

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Randomized phase II trial of S-1 plus cisplatin or docetaxel plus cisplatin with concurrent thoracic radiotherapy for inoperable stage III non-small cell lung cancer (TORG1018): An interim report

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Background: Concurrent chemoradiotherapy (CCRT) is the current standard treatment for inoperable stage III non-small cell lung cancer (NSCLC), and a clearly superior regimen has not yet been identified. This study was conducted to evaluate cisplatin with S-1 (SP) or docetaxel (DP) with concurrent thoracic radiotherapy, in patients with inoperable stage III NSCLC.

Methods: In this open-label, non-comparative phase II trial, patients with inoperable stage III NSCLC were randomized (1:1) to SP (S 140 mg/m2 twice a day on days 1-14 and 29-42, and cisplatin 60 mg/m2 on days 1 and 29) or DP (docetaxel 50 mg/m2 and cisplatin 60 mg/m2 on days 1 and 29). In both arms, concurrent radiotherapy was started on day 1 (total 60 Gy in 30 fractions). After CCRT, patients in each group received two additional cycles of consolidation chemotherapy with the same regimen as that for the CCRT part. The primary endpoint was the 2-year overall survival (OS) rate, and secondary endpoints were OS, progression-free survival (PFS), toxicity profile, dose intensity and objective response rate (ORR).

Results: Between May 2011 and August 2014, 110 patients from 19 institutions were enrolled. Finally, 106 patients (63 in each arm) were evaluated for efficacy and safety. The patient characteristics were: male/female, 83/23; median age, 65 (range 42-74) yr; ECOG performance status 0/1, 57/43; IIA/IIB, 59/41. After a median follow-up of 23.1 months, ORR and median PFS were 71.7% (95%CI: 57.7-83.2) and 11.5 months (95% CI: 9.0-14.1) in the SP arm, and 67.9% (95%CI: 53.7-80.1) and 17.2 months (95% CI: 9.6-24.0) in the DP arm, respectively. Grade 3-4 leukopenia (34.0%/62.3%) and neutropenia (28.3%/56.6%) were significantly higher in the DP arm than in the SP arm. Incidences of non-hematological toxicity including febrile neutropenia, anemia, nausea, diarrhea, radiation pneumonitis and esophagitis tended to be high in the DP arm. No treatment-related death occurred.

Conclusions: At this preliminary stage, it appears that although the DP arm may have more toxic effects than the SP arm, it has a favorable PFS. The OS data will be available soon.

Clinical trial identification: UM1180005993

Legal entity responsible for the study: Thoracic Oncology Research Group

Funding: Thoracic Oncology Research Group

Disclosure: T. Shimokawa, H. Okamoto: I have received research funding from Takeda, MSD, Ono, Astrozenea, Merck, Chugai, Taiho, Bristol, Eli Lily and Pangex. K. Kubota: Honorary: Taiho, Chugai, Eli Lily. Y. Takeda: Grants and lecture fees from Chugai, Bristol-Myers Squibb, Kyowa Hakko Kirin, Merck Serono, Boehringer Ingelheim Japan, Ono, Taiho, grants from Eli Lily Japan, Mochida, lecture fees from AstaZenea Japan, outside the submitted work. Y. Hosomi: Speaker fees from honoraria from Chugai, Eli Lilly Japan, AstraZenea, Taiho and Ono, outside the submitted work. T. Kato: Taiho pharmaceuticals: Lecture fee and research grant. T. Yamanaka: Honorary: Taiho, Chugai, Taikei. All other authors have declared no conflicts of interest.

A phase I / II trial of pemetrexed plus radiation therapy in elderly patients with locally advanced NSCLC

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Background: Although the clinical efficacy of radiation therapy (RT) has been demonstrated in elderly patients with locally advanced non-small cell lung cancer (NSCLC), the combination of pemetrexed (PEM) and RT has not been examined in clinical trials yet. Therefore, we conducted a phase I / II study to evaluate the appropriate PEM dose, efficacy and safety of PEM plus RT in elderly patients with locally advanced NSCLC.

Methods: Eligibility criteria included performance status (PS) 0-2, aged 71 years or older, pathologically confirmed NSCLC, locally advanced stage (IIA / IIB), adequate organ function, and written informed consent. Patients received PEM (500mg/m2 on day of a 28-day cycle, 4 course) and RT (total 60 Gy / 30 fractions over 6 weeks). The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and adverse events (AEs).

Results: A total of 41 patients (4 patients in phase I, 37 patients in phase II) were enrolled. Median age was 79 years old (range 71-87) and 31 patients were male. Eighteen patients were squamous cell carcinoma, 27 of 41 patients were stage IIA, and 38 patients were PS 0-1. ORR was 80.5%. Median OS was 24.6 months and median PFS was 6.8 months. There were 2 treatment related deaths, caused by RT pneumonitis in one patient and severe infection in one patient. Common hematological AEs were leukopenia and neutropenia, whereas, common non-hematological AEs were anorexia and constipation. Intestinal lung disease caused by PEM developed in 3 patients. RT related AEs were mainly observed, including radiation esophagitis (grade 1: 22 patients, 2: 6 patients, 3: 1 patient) and RT pneumonitis (grade 1: 11 patients, 2: 14 patients, 3: 7 patients, 5: 1 patient).

Conclusions: This combination treatment shows promising activity, but RT related toxicities were relatively severe. Therefore, the use of this treatment require close caution for elderly patients.

Clinical trial identification: UM1180005036

Legal entity responsible for the study: Shinni Atagi

Funding: National hospital organization network funding

Disclosure: S. Atagi: Honorary: Eli Lilly Japan, Chugai, Taiho, Boehringer Ingelheim, Pfizer Japan, Ono, and AstaZenea. Research Funding: Chugai, Pfizer, Ono, Merck Serono, Boehringer Ingelheim, AstaZenea, Taiho, Yakult, Eli Lilly, N. Nagomi: Honorary: Chugai, Taihou, Eli Lilly, Pfizer, AstaZenea, Ono, R.M.S, Nippon Boehringer. All other authors have declared no conflicts of interest.
Background: The influence of the recurrence pattern on outcome of patients (pts) with stage III NSCLC following definitive chemo-radiotherapy (CRT) has been scarcely addressed in the literature. The aim of this study was to assess the relevance of oligoprogression (OP) in this clinical setting.

Methods: Pts diagnosed with stage III NSCLC who underwent concurrent CRT from May 2010 to 2014 at the Catalan Institute of Oncology were retrospectively studied. The recurrence pattern at the first progression was recorded. OP was defined as a single metastatic site with no more than 3 lesions. Overall Survival (OS), Progression-Free Survival (PFS) and Postprogression OS (PPO) were plotted using the Kaplan Meier method and multivariable Cox proportional hazards models were developed.

Results: From 171 pts median age 62 (37-74) male 87%, ECOG ≤ 1 92%, smoking status: current 49%, former 44, never 5%; histology: adenocarcinoma (ADC) 34%, squamous (SC) 43%, NSCLC (NS > large cell) 23%; Stage IIIA 51%, IIIB 49%, ≥N1 22.1%, ≥N2 19%. Platinum doublet CT: Capmatinib 6%, Carboplatin 38%. Rate between 60 and 70 CgY/year. At a median follow-up of 48 months (m), 108 patients (63%) developed OP. The OPFS was 13m (95% CI 10-16) and the OPOS was 28m (95% CI 26-31) for those who received 2nd line treatment (n = 77, 72%), vs 13m for those without treatment (n = 31, 28%). PFS and OS for patients who received 2nd line treatment were 40% and 30%, respectively. In the univariate analysis of OP, OP stood out as a favourable prognostic factor (HR = 0.36, 95% CI 0.17-0.74) independently of age, stage, histology, ECOG PS, smoking history and platinum doublet.

Conclusions: In this cohort, the frequency of OP was remarkable and associated with improved OS. Pts with OP that might benefit from salvage therapies should be better characterized and proactively detected during follow-up after definitive CRT.

Legal entity responsible for the study: Institut Català d’Oncologia

Funding: Institut Català d’Oncologia

Disclosure: All authors have declared no conflicts of interest.

**1193P** Comparison of combined chemoradiotherapy regimens; Paclitaxel plus carboplatin and cisplatin plus etoposide for locally advanced non-small-cell lung cancer: A randomized phase III trial

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Background: The optimal chemotherapy regimen to use with radiotherapy in stage III non–small-cell lung cancer (NSCLC) is unknown. This phase III comparative randomized trial was conducted to determine the optimal chemotherapy regimen with standard daily concurrent thoracic radiation therapy (CTRT), in patients with locally advanced unresected stage III NSCLC.

Methods: We recruited 108 patients aged 18–72 years with stage III, histologically confirmed NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, an estimated life expectancy of greater than 3 months, and adequate organ function from January 2011 to December 2014. Patients were randomised (1:1) to paclitaxel plus carboplatin and cisplatin plus etoposide arms.

Results: Patients with unresected stages IIIA and IIIB NSCLC received carboplatin (AUC = 2) and paclitaxel (45 mg/m2) given weekly with CTRT (63 Gy) followed by two cycles of consolidation therapy (carboplatin AUC = 6, paclitaxel 200 mg/m2) (arm CP) and cisplatin (50 mg/m2) on days 1, 8, 29, and 36 plus etoposide (50 mg/m2) daily on days 1 to 5 and 29 to 33 with CTRT followed by consolidation cisplatin plus etoposide (arm EP) were included. Ninety nine eligible patients were evaluated. With median follow-up time of 39.4 months, median overall survival was 17.1 and 16.6 months for arms CP and EP, respectively (R = 0.279). But patients in arm CP compared with patients in arm EP, had more grade 4 neutropenia (18.1% vs 11.1%, p < 0.001), grade 3–4 mucositis/esophagitis (22.2% vs 12.1%, p = 0.001) and acute kidney disease (27.2% vs 14.1%, p = 0.001).

Conclusions: In patients with stage III NSCLC treated with cisplatin plus etoposide and carboplatin plus paclitaxel showed similar overall survival, but cisplatin plus etoposide arm was associated with increased toxicity.
Methods: Patients received 3 cycles of DOC (60mg/m², d1) plus CDDP (80mg/m², d1), q3-4w, and subsequently received S-1 at 40mg/m² twice daily for 14 consecutive days. Patients received 3 cycles of DOC (60mg/m², d1) plus CDDP (80mg/m², d1), q3-4w, and subsequently received S-1 at 40mg/m² twice daily for 14 consecutive days.

Results: A total of 328 and 314 patients were randomized to ABP 215 (Arm 1) and bevacizumab (Arm 2) groups; the groups were balanced in demographic and baseline characteristics. There were 128 (39.0%) responders in Arm 1 and 131 (41.7%) in Arm 2.

Conclusions: Pathologic response can be a surrogate marker for survival in patients who underwent surgery after neoadjuvant chemotherapy.

Clinical trial identification: UMIN000004278

Legal entity responsible for the study: Morthito Okada

Funding: Hiroshima University

Disclosure: All authors have declared no conflicts of interest.

First site of relapse can predict different clinical courses in recurrent stage II/IIIA non-small cell lung cancer after definitive chemoradiotherapy

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Background: The standard treatment for stage IIA non-small cell lung cancer (NSCLC) is definitive chemoradiotherapy (dCRT). However, approximately 80% of patients experience relapse, resulting in a poor prognosis. The aim of this study was to evaluate the relapse patterns of patients with stage IIA NSCLC after dCRT and their clinical courses.

Methods: A retrospective review of patients treated for stage IIA NSCLC at the National Cancer Center between 2002 and 2011 was performed. Data on patients’ characteristics, the first relapse site after dCRT (inside or outside of the radiotherapy field), presence or absence of brain metastasis (BM), salvage treatment, and the disease progression site after salvage treatment were collected. The post-progression overall survival (PPOS) was evaluated using the Kaplan-Meier method.

Results: Among the 152 patients who were treated with dCRT, 115 (76%) relapsed and were included in this analysis. Of these, initial recurrence (IR) and brain metastasis (BM) as a first relapse were observed in 30 (26%) and 14 (12%) patients, respectively. The other 71 patients (62%) experienced mixed recurrences (MR) including infield and distant metastases.

Conclusions: Pathologic response can be a surrogate marker for survival in patients who underwent surgery after neoadjuvant chemotherapy.
surgery were performed in 83 (72%) patients. In patients with IR, 2 patients (7%) underwent surgery, and the others were treated using chemotherapy. The median PPS (mPPS) and the 3-year PPS (3yPPS) rate in patients with IR were 16.8 months and 0%, respectively. All the patients with BM underwent local radiotherapy. The mPPS and the 3yPPS rate in patients with BM were 25.3 months and 39.3%, respectively. After salvage treatment, 17 (56%) of the 30 patients with IR experienced isolated disease progression, and 10 (71%) of the 14 patients with BM developed CNS progression. In patients with MR, the mPPS and 3yPPS rate were 10.9 months and 17.2%, respectively.

**Conclusions:** Patients with IR tended to have a poorer prognosis than those with other patterns of relapse because of persistent local disease progression, while patients with BM experienced a better survival outcome. The development of an effective salvage therapy taking the recurrence pattern into account is mandatory.

**Clinical trial identification:** The study protocol was approved by the institutional review boards of the National Cancer Center Hospital (number: 2015-335).

**Legal entity responsible for the study:** National Cancer Center

**Funding:** N/A

**Disclosure:** H. Horinouchi: Corporate-sponsored research: Taiho, Merck Serono, MSD. Astellas, Novartis. H. Nokihara: Honoraria: Boehringer Ingelheim, Taiho, AstraZeneca, Ono, Sanofi, Lilly Research Funding. Merck, Pfizer, Taiho, Eisai, Chugai, Lilly, Novartis, Daichi Sankyo, GlaxoSmithKline, Yakult, Quintiles, Astellas, AstraZeneca, Boehringer Ingelheim, Ono. N. Yamamoto: Research funds (as institutions): Quintiles, Astellas, Chugai, Eisai, Taiho, BMS, Pfizer, Novartis, Daichi Sankyo, Boehringer Ingelheim, Kyowa Hakko Kirin. Honoraria: AstraZeneca, Pfizer, Lilly, Chugai. Y. Ohe: Research: AstraZeneca, Chugai, Lilly, Ono, BMS, Kyorin, Dainippon-Sumitomo, Pfizer, Taiho, Novartis, Merc honoraria: AstraZeneca, Chugai, Lilly, Daichi-Sankyo, Nyippekeayaku, Boehringer Ingelheim, Bayer, MSD, Taiho, Clavio, Sanofi. All other authors have declared no conflicts of interest.

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**Cardiotoxic effects of gemcitabine/cisplatin vs paclitaxel/carboplatin first-line chemotherapy in patients with advanced non-small cell lung cancer**

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**Background:** Introduction: The aim of this study was to establish the frequency of cardiotoxicity in the patients treated with the first-line chemotherapy (gemcitabine/cisplatin and paclitaxel/carboplatin), with or without the history of cardiovascular co-morbidities.

**Methods:** This prospective study included 240 patients with cytologically or histopathologically confirmed NSCLC at the clinical stages III and IV, divided into subgroups according to the type of chemotherapy and the presence of cardiovascular co-morbidities. Physical examination, electrocardiogram and N-proBNP and troponin T levels were performed before and after the application of each cycle of chemotherapy. Echocardiography was performed before and after chemotherapy, as well as in the follow-up examinations every three months, a total of one year. Cardiac toxicity was determined based on the presence of cardiovascular symptoms, changes in the electrocardiogram, elevated levels of NT-proBNP and troponin T and a decrease in left ventricular ejection fraction.

**Results:** In the study group 184 patients (76.7%) were male. The most frequent was adenocarcinoma, in 120 patients (50%). Most common cardiovascular toxic effects were increase in the level of NT-proBNP (44.85%), cardiac arrhythmias (26.18%), venous thromboembolism (19.9%) and decreased left ventricular ejection fraction (6.8%). Patients treated with the first-line chemotherapy gemcitabine/cisplatin developed cardiotoxicity more frequently if they had a former history of cardiovascular diseases, but without statistical significance. Patients treated with the first-line chemotherapy paclitaxel/carboplatin developed cardiotoxicity more frequently if they had a former history of cardiovascular diseases, and the statistical significance was registered at the first follow-up examination in stage III NSCLC patients (p = 0.037).

**Conclusions:** Chemotherapy induced cardiotoxicity frequently occurs in patients with cardiovascular co-morbidities. Balance between the effectiveness of chemotherapy and the risk of cardiotoxicity requires close cooperation oncoloģists and cardiologists, with the aim of creating individual therapy for each patient.

**Legal entity responsible for the study:** N/A

**Funding:** The Faculty of Medicine Novi Sad

**Disclosure:** All authors have declared no conflicts of interest.

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**Table: 1200P**

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<th>PET Use</th>
<th>PFS and OS by PET Use</th>
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<td>Intent-to-Treat Patients PET Scan</td>
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<td>Yes (N = 491)</td>
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<tr>
<td>Median OS, months</td>
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<tr>
<td>95% CI</td>
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<tr>
<td>HR (95% CI)</td>
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<td>Median PFS, months</td>
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<tr>
<td>95% CI</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.56, 0.93)</td>
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**Conclusions:** Both patients who had PET scans showed a numerically longer OS in the subgroup of patients with PET scans, compared to patients with conventional staging, which was consistent with improved survival due to stage migration. The magnitude of differences in OS and PFS based on PET is a reminder of the potential of factors other than the therapeutic intervention to affect outcomes.

**Clinical trial identification:** NCT00686959

**Legal entity responsible for the study:** Eli Lilly and Company

**Funding:** Eli Lilly and Company

**Disclosure:** N. Iosec: Employee of Eli Lilly Canada Inc. R. Govindan: Employee of Boehringer Ingelheim, GSK, Celgene, Roche, Bayer, Genentech, AstraZeneca. A.M. Hossain: Employed by Eli Lilly and Company. R. San Antonio, N. Choukou: Employee of Eli Lilly and Company. E. Vokes: Amgen, AstraZeneca, Boehringer Ingelheim, Celgene, Lilly, Genentech, Merck, Synta, VentiRx. S. Senan: Lilly, Varian Medical Systems. All authors have declared no conflicts of interest.

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**The impact of staging by positron emission tomography (PET) on overall survival (OS) and progression-free survival (PFS) in the phase III PROCLAIM study**

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**Background:** Real-world evidence of the significant impact of PET staging on survival outcomes because of stage migration (upstaging) has been previously documented. However, the effect of stage migration as a result of PET has rarely been measured in randomized trials in the locally advanced stage IIIA/B setting. Here, we report the results from post-hoc subgroup analyses based on PET scan use in non-small cell lung cancer (NSCLC) patients in the PROCLAIM study.

**Methods:** The intent-to-treat (ITT) population of 598 patients with stage IIIA/B nonsquamous NSCLC were randomized to either pemetrexed (Pem) plus cisplatin (Cis) and concurrent radiotherapy (RT) for 3 cycles, followed by 4 cycles of Pem consolidation, or eribulin plus Cis and concurrent RT for 2 cycles, followed by a consolidation platinum-based doublet regimen for up to 2 cycles. PET scan (yes vs no) was one of the stratification factors since its use was not required per protocol. Subgroup analyses (yes vs no PET) of OS and PFS was conducted on the ITT population regardless of treatment since the study did not demonstrate superior efficacy for either arm. Kaplan-Meier methods and Cox regression models were used to estimate hazard ratios.

**Results:** Of the 598 patients, the majority (n = 491, 82.1%) had PET scan staging performed. The OS and PFS by PET scan use are presented in the table. In addition, results of subgroup analyses for each treatment arm were consistent with those of the ITT population.
NSCLC, metastatic

12010 Gefitinib chemotherapy vs chemotherapy in EGFR mutation-positive NSCLC after progression on 1st line gefitinib (IMPRESS study): Final overall survival (OS) analysis

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Background: IMPRESS (NCT01544179) evaluated continuation of gefitinib plus cisplatin/pemetrexed (cis/pem) in patients (pts) with acquired resistance to 1st line gefitinib. Primary results (progression-free survival [PFS]) confirmed that continuing gefitinib in addition to cis/pem is of no clinical benefit. We present final OS data.

Methods: Pts (age ≥18 years, chemo-naïve, locally advanced/metastatic NSCLC with activating EGFR mutation, progression on 1st line gefitinib) from 61 centres (Europe/Asia Pacific) were randomised to G or P (gefitinib 250 mg/day or placebo; plus cis 75 mg/m²/pem 500 mg/m²). Primary endpoint: OS. Secondary endpoints included: OS, progression-free survival (PFS), safety and tolerability. In pre-planned biomarker analyses, EGFR T790M mutation status was analysed via plasma circulating free tumour-derived DNA.

Results: A total of 265 pts were randomised (G 133; P 132) and followed until 175 deaths. Final OS analysis showed HR 1.15, 95% CI 0.96–1.38, p = 0.152. Median OS was 18.1 months longer for G vs P (18.3 vs 10.2 months).

Conclusions: Final IMPRESS OS data indicate that pts with acquired resistance to 1st line gefitinib should not continue to receive the TKI plus doublet chemotherapy beyond progression, due to the observed detrimental effect on OS. Exploratory plasma biomarker analyses suggest that this effect may be driven by T790M-positive status; inconclusive data in the T790M-negative subgroup warrant further investigation.

Clinical trial identification: NCT01544179

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca


Table: 12010

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<th>nN</th>
<th>HR</th>
<th>95% CI</th>
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<tr>
<td>Overall</td>
<td></td>
<td>1.15</td>
<td>0.96–1.38</td>
<td>13.4 vs 19.5</td>
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<tr>
<td>Overall with additional covariates</td>
<td></td>
<td>1.15</td>
<td>1.09–1.34</td>
<td>13.7 vs 19.4</td>
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<td>Presence/absence of brain metastases and T790M mutation status (positive/negative/unknown) at baseline</td>
<td></td>
<td>1.15</td>
<td>1.09–1.34</td>
<td>13.7 vs 19.4</td>
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<td>1.19</td>
<td>0.99–1.43</td>
<td>13.5 vs 19.3</td>
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- < 0.05% AF T790M and ≥0.02% AF exon 19 deletion or L858R mutation (T790M mutation-negative, senstising mutation-positive)
- c.0.02% AF T790M and ≥0.02% AF exon 19 deletion or L858R mutation (T790M mutation-negative, senstising mutation-positive)

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Overall, 11.3% of pts discontinued due to AEs, with no particular AE predominating. The most frequently reported AEs were gastrointestinal (GI): diarrhoea (85.5%), followed by rash (35.9%), fatigue (33.2%), nausea (28.1%), nausea (22.0%), constipation (21.5%), and dry skin (19.3%). Median duration of AEs was 13 days (range 1-186 days) for diarrhoea, 14 days (range 1-185 days) for rash, and 13 days (range 1-186 days) for fatigue.

Table: 1202O

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<td>PFS (faster line)</td>
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<td>4.3</td>
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<td>DCR (TKI)</td>
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</table>

Conclusions: Common and non-common EGFR mutations presented different clinical characteristics. Among common mutations, erlotinib had better outcomes. Clinical trial identification: NCT01700582

Legal entity responsible for the study: N/A

Funding: INCA, AstraZeneca

Disclosure: C. Leduc, Chugai. M. Beau-Faller, AstraZeneca, Boerhinger-Ingelheim, Roche. All other authors have declared no conflicts of interest.

1208O

**Phase 2 study of ceritinib in ALK-rearranged patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC): whole body responses in the overall population and by baseline brain metastases status (BM)**


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Background: In the pivotal ASCEND-1 study, ceritinib showed whole body efficacy in ALK+NSCLC (including those with baseline BM), most of whom had received multiple prior therapies, median progression-free survival (mPFS) was 18.4 months. The ASCEND-3 single-arm, open-label multicentre study evaluated the efficacy and safety of ceritinib in previously treated ALK+naive pts with ALK+ NSCLC (NCT01685138).

Methods: Pts enrolled worldwide received oral ceritinib 750 mg/d (fasted) from 21 Jan 2015. Patients separated by brain metastases status at study entry were evaluated for whole body responses.

Results: Of 124 pts receiving ceritinib, 122 (98.4%) had received prior antineoplastic regimens (with 31 [25%] receiving ≥3). Of the 124 pts, 49 (39.5%) had baseline BM. Whole body ORR (CR + PR) was 63.3% (95% CI 48.3, 76.6) and median DOR was 22.1 months (95% CI 14.8, NE).

By Investigator

<table>
<thead>
<tr>
<th>ORR (CR + PR), n (%)</th>
<th>31 (63.3)</th>
<th>43 (87.8)</th>
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</thead>
<tbody>
<tr>
<td>(95% CI)</td>
<td>48 (74.0)</td>
<td>69 (92.0)</td>
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<tr>
<td>By BM status</td>
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</table>

All patients N = 124

Clinical trial identification: NCT01685138

Legal entity responsible for the study: Novartis Pharmaceutical Corporation

Table: 1208O

<table>
<thead>
<tr>
<th></th>
<th>Wild-type</th>
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<tr>
<td>OS, months</td>
<td>11.8</td>
<td>14.2</td>
<td>14.0</td>
<td>12.4</td>
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<tr>
<td>PFS (faster line)</td>
<td>7.2</td>
<td>4.5</td>
<td>4.3</td>
<td>3.7</td>
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<td>(n = 35)</td>
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</tbody>
</table>

LUREST study: Phase 2 study of vandetanib in patients with advanced RET-rearranged non-small cell lung cancer (NSCLC)


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Background: RET rearrangements were identified as a new rare oncogenic alteration in NSCLC. Vandetanib is a multi-targeted tyrosine kinase inhibitor having RET kinase inhibitory activity.

Methods: This was a multicenter, single-arm phase 2 study to evaluate the efficacy and safety of vandetanib in patients with advanced RET-rearranged NSCLC who failed at least one prior chemotherapy. Vandetanib was administered orally at 300 mg once daily in 28-day cycles. RET-positive patients were screened by a nationwide genomic screening program with approximately 200 institutions in Japan participating in a durable mPFS of 18.4 months (95% CI 14.8, NE). The primary endpoint was the independently assessed objective response rate (ORR). Exploratory subgroup analyses for ORR and progression-free survival (PFS) were performed with the factors including sex, smoking status, and type of RET fusions.
Phase 2 study of lenvatinib (LN) in patients (Pts) with RET-fusion-positive adenocarcinoma of the lung


Background: Adenocarcinoma, a type of non-small cell lung carcinoma (NSCLC), is one of the most common forms of lung cancer. RET fusions activate RET kinase and occur in 1% to 2% of these pts. LN, a multitasking inhibitor whose targets include RET, may be a treatment option for pts with NSCLC.

Methods: This open label, phase 2 study enrolled pts with RET-positive lung adenocarcinoma. Pts received LN 24 mg/d in 28-d cycles until disease progression or unacceptable toxicity. Notably, pts may have received prior RET-targeted therapy. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR; ≥ 50% ORR), and ROS1-EZR. The median progression-free survival was 19.3 months (95% CI, 12.7-7.2-not reached), and the median overall survival was not reached at the time of the data cut-off. Of 5 patients with retrospectively confirmed brain metastases, intracranial response rates were 80% (range, 2-7) and 17 (53%) patients had received three or more lines of chemotherapy. The most common TEAEs included hypertension (68%), nausea (60%), dose reduction, and dose interruption occurred in 5 (20%), 16 (64%), and 19 (76%) pts, respectively. The most common SEAEs included anemia (68%), neutropenia (60%), decreased appetite (52%), diarrhea (52%), proteinuria (48%), and vomiting (44%).

Results: With screening of 1536 advanced NSCLC patients in the LC-SCRUM-Japan, 34 patients presented with RET-positive NSCLC. Of these pts, 32 (94%) presented with lung adenocarcinoma. 25 of these pts were enrolled in the 12-month extension of the phase 2 study.

Table: 1204PD

<table>
<thead>
<tr>
<th>Prior RET therapy</th>
<th>All Pts n = 25</th>
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<tbody>
<tr>
<td>ORR, * (n)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>7.3 (1.6-10.2)</td>
</tr>
<tr>
<td>Median OS (95% CI), months</td>
<td>NE (5.8-NE)</td>
</tr>
<tr>
<td>DCR, (n)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>CBR, (n)</td>
<td>4 (57)</td>
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</table>

*CI confidence interval; DCR, disease control rate defined as CR + PR + SD lasting ≥ 7 weeks; NE, not evaluable. *All confirmed PRs

Conclusions: LN showed promising clinical activity in pts with RET-positive NSCLC. For most pts, toxicities were manageable with dose modification. These results provide support for LN as a potential treatment for RET-positive NSCLC.

Clinical trial identification: NCT01877083

Legal entity responsible for the study: Eisai Inc.

Funding: Eisai Inc.


Ceritinib in ROS1-rearranged non-small-cell lung cancer: a Korean nationwide phase II study


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Background: ROS1 rearrangement is a distinct molecular subset of non-small-cell lung cancer (NSCLC). We investigated the efficacy and safety of ceritinib in patients with ROS1-rearranged NSCLC.

Methods: We enrolled 32 patients with advanced NSCLC who tested positive for ROS1 rearrangement by fluorescent in situ hybridization (FISH). ROS1 immunohistochemistry (IHC) and next-generation sequencing (NGS) were performed in available tumor samples. The primary endpoint was objective response rate (ORR) by central independent radiologic review. The secondary endpoints included disease control rate (DCR), duration of response, progression-free survival (PFS), overall survival (OS), toxicity and concordance between FISH, IHC and NGS.

Results: Between June 7, 2013, and February 12, 2016, a total of 407 patients underwent ROS1 prescreening, and 32 ROS1+ (by FISH) patients were enrolled. The median age of all patients was 62 years, and the majority of patients (84%) were never smokers, and all had adenocarcinoma histology. The median time from initial diagnosis to ROS1 testing was 3 months (range, 2-7) and 17 (53%) patients had received three or more lines of chemotherapy. At the time of the data cut-off (April 18, 2016), the median follow-up was 7.5 months, and 15 (47%) patients had discontinued treatment. The ORR was 63% (95% CI, 45.7-79.3), with 1 complete response and 19 partial responses. The median duration of response was 10.0 months (range, 0.4-18.4+). Among 11 tumors that were tested by NGS, we identified 7 ROS1 fusion partners including ROS1-CD74, ROS1-SLC3A4, and ROS1-EZR. The median progression-free survival was 19.3 months (95% CI, 7.2-not reached), and the median overall survival was not reached at the time of the data cut-off. Of 5 patients with retrospectively confirmed brain metastases, intracranial disease control was reported in 3 patients (60%). Gastrointestinal adverse events, mostly grade 1-2, were the most frequent adverse events (80%); these events were manageable.

Conclusions: Ceritinib demonstrated potent clinical activity in patients with advanced, ROS1-rearranged NSCLC, who received at least one prior line of platinum-based chemotherapy. ROS1 rearrangement defines a second molecular subgroup of NSCLC for which ceritinib is highly active.

Clinical trial identification: NCT01964157

Legal entity responsible for the study: N/A

Funding: Novartis Pharmaceutical

Disclosure: All authors have declared no conflicts of interest.
Crizotinib in advanced ROS1-rearranged non-small cell lung cancer (NSCLC): updated results from PROFILE 1001


1Massachusetts General Hospital Cancer Center, Massachusetts General Hospital, Boston, MA, USA, 2Memorial Sloan-Kettering Cancer Center, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, 3Department of Internal Medicine, Seoul National University Hospital (SNUH)-Yongon Campus, Seoul, Republic of Korea, 4Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, 5Cancer Center, University of Colorado, Aurora, CO, USA, 6Early Drug Development Centre, Dana-Farber Cancer Institute, Boston, MA, USA, 7Cancer Center, University of California at Irvine, University of California at Irvine, Irvine, CA, USA, 8Cancer Center and Comprehensive Cancer Treatment Centers of America-Western Regional Medical Center, Goodyear, AZ, USA, 9University of California at Irvine, University of California at Irvine, Irvine, CA, USA, 10Cancer Center, University of Colorado, Aurora, CO, USA

Background: In the phase I study PROFILE 1001, crizotinib showed marked antitumor activity in advanced ROS1-rearranged NSCLC (Shaw, N Engl J Med 2014). We present updated data for 53 patients (pts) with ROS1-rearranged NSCLC from this ongoing study (NCT01585195).

Methods: ROS1 status was determined by break-apart FISH test or RT-PCR test. All pts received crizotinib at a starting dose of 250 mg orally twice daily.

Results: Fifty-three pts enrolled and were treated with crizotinib for a median treatment duration of 23.2 months. All were included in the efficacy and safety analyses. At data cutoff (November 30, 2014), treatment was ongoing in 25 pts (47%). The median age of pts was 55 years, 57% were female, and 57% and 40% were white and Asian, respectively; all were never or former smokers. The objective response rate (ORR) was 70% (95% CI: 56, 82), which included five complete responses and 32 partial responses; 11 pts had stable disease. By independent radiology review (n = 50), ORR was 66% (95% CI: 51, 79). Responses were durable (median duration of response not reached [NR]; 95% CI: 15.2, NR). ORR was consistent across baseline and disease characteristics, and appeared independent of the percentage of ROS1-rearranged cells. Median progression-free survival was 19.3 months (95% CI: 14.8, NR). At a median follow-up of 24.5 months, median overall survival was NR, the probabilities of survival at 6 and 12 months were 91% (95% CI: 79, 96) and 79% (95% CI: 65, 88), respectively. The safety profile was similar to that of crizotinib in pts with ALK-positive NSCLC.

The most common treatment-related adverse events (TRAEs) were vision disorder (85%), nausea (49%), edema (45%), diarrhea (42%), and vomiting (38%); mainly grade 1 or 2 in severity. The most common grade 3 TRAEs were hypophosphatemia (13%), neutropenia (9%), and elevated transaminases (4%), and there were no grade 4 TRAEs.

Of 16 deaths on study, none were attributed to crizotinib. Treatment-emergent AEs (excluding disease progression; any cause) in all pts were 14.5 months and 12.9 months, respectively; in CRZ-naive pts, medians were not reached. Treatment-emergent adverse events (AEs) in ≥50% of all pts (most grade 1/2): nausea 51%, fatigue 42%, diarrhea 41%, headache 34%, cough 33%. Serious treatment-emergent AEs (excluding disease progression, any cause) in 22% of all pts: dyspnea 7%, pneumonia 7%, hypoxia 5%, pulmonary embolism 3%, malignant pericardial effusion 2%, pneumonitis 2%. Of 137 pts, 14 (10%) discontinued due to an AE.

Conclusions: These updated data confirm the clinically meaningful benefit and safety of crizotinib in pts with advanced ROS1-rearranged NSCLC.

Clinical trial identification: Clinicaltrials.gov: NCT01585195

Legal entity responsible for the study: N/A

Funding: Pfizer

Disclosure: G.J. Riley is a consultant for Pfizer. Y-J. Bang received research funding from Pfizer to their institution.

Brigatinnib (BRG) in patients (Pts) with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) in a phase 1/2 trial

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Background: BRG, an investigational oral ALK inhibitor with preclinical activity against ALK mutants resistant to crizotinib (CRZ) and other ALK inhibitors, was studied in pts with advanced malignancies, including ALK+-NSCLC.

Methods: 137 pts (ALK+-NSCLC, n = 79) received oral BRG (30–300 mg/d) in an ongoing phase 1/2, single-arm, open-label, multicenter trial (NCT01449461). We report activity by RECIST v1.1 (in ALK+-NSCLC pts) and safety in all pts.

Results: As of 16 Nov 2015, 36/79 (46%) ALK+-NSCLC pts (median age 54 years, 49% female, 90% with prior CRZ) continued to receive BRG. Median time on treatment was 17.8 months (1 day to 44.4 months). 5/72 (7%) pts with prior CRZ and 8/88 (9%) CRZ-naïve pts achieved an objective response (see table). In pts with prior CRZ, median duration of response in confirmed responders and progression-free survival in all pts were 14.5 months and 12.9 months, respectively; in CRZ-naive pts, medians were not reached.

Treatment-emergent AEs (excluding disease progression; any cause) in 22% of all pts: dyspnea 7%, pneumonia 7%, hypoxia 5%, pulmonary embolism 3%, malignant pericardial effusion 2%, pneumonitis 2%. Of 137 pts, 14 (10%) discontinued due to an AE.

Conclusions: BRG had substantial antitumor activity in ALK+-NSCLC pts and an acceptable safety profile in this study. A pivotal, randomized, phase 2 trial of BRG in CRZ-resistant ALK+-NSCLC (ALTa) evaluating 90 mg qd vs 180 mg qd with a 7-day lead-in at 90 mg is ongoing.

Legal entity responsible for the study: ARIAD Pharmaceuticals, Inc.

Funding: ARIAD Pharmaceuticals, Inc.

Disclosure: L. Bazhenova: Stock and other ownership interests (Epic Sciences), honoraria (Novartis), consulting or advisory role (AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, Clovis Oncology, Genoptix, Heat Biologics, Pfizer, Roche/Genentech, Seattle Genetics, and Trovagene), speakers bureau (AstraZeneca, Novartis, Pfizer, Roche/Genentech). S. Gettinger: Consulting or advisory role (ARIAD, BMS, Janssen), research funding (ARIAD, AstraZeneca/MedImmune, BMS, Boehringer Ingelheim, Incyte, Pfizer, Roche/Genentech). K. Gold: Honoraria (BMS, Roche), consulting or advisory role (Pfizer), research funding (ARIAD, AstraZeneca, Lilly, Merck, MPM, Roche/Genentech). C. Langer: Honoraria (BMS, Lilly/ImClone, Roche/Genentech), consulting or advisory role (Abbott, ARIAD, AstraZeneca, Bayer/Oryx, BMS, Cancer Support Community, Celgene, Clovis Oncology, Lilly/ImClone, Merck, Millennium, Roche/Genentech), research funding (Advantagene, ARIAD, Celgene, Clovis Oncology, GSK, Inovio, Merck, Roche/Genentech). A. Shaw: Honoraria (Novartis, Pfizer, Roche), consulting or advisory role (ARIAD, Bluepain Medicines, Daiichi Sankyo, EMD Serono, Ignyta, Novartis, Pfizer, Roche/Genentech, Taiho), research funding (ARIAD, Ignyta, Novartis, Pfizer). G. Weiss: Employment (Cancer Treatment Centers of America), consulting or advisory role (Blend Therapeutics, Paradigm, Pharmatech), speakers bureau (Amgen, Celgene, Medisce, Merc, Novartis, Pfizer, Quintiles), travel, accommodations, expenses (Cambridge Healthtech Institute, Nantworks, Pharmatech). J. Haney, V. Rivera, F. Haluska, D. Kerstein: Employment, AstraZeneca, BMS, Boehringer Ingelheim, Clovis Oncology, Genoptix, Heat Biologics, Pfizer, Roche/Genentech, Seattle Genetics, and Trovagene.

Table: 1207PD Response in ALK+-NSCLC Pts, With Prior CRZ Exposure (All and at Doses Explored in Phase 2) and CRZ-Naive

<table>
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<tr>
<th>CRZ Exposure</th>
<th>CRZ-Naive</th>
<th>CRZ-Naive</th>
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<tbody>
<tr>
<td>Prior CRZ</td>
<td>180 mg/d</td>
<td>180 mg/d</td>
</tr>
<tr>
<td>90 mg qd</td>
<td>20 (80)</td>
<td>15 (65)</td>
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<tr>
<td>90 mg qd</td>
<td>2 (8)</td>
<td>2 (9)</td>
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<tr>
<td>180 mg/qd</td>
<td>18 (72)</td>
<td>13 (57)</td>
</tr>
<tr>
<td>90 mg qd</td>
<td>19 (76)</td>
<td>14 (61)</td>
</tr>
<tr>
<td>180 mg/qd</td>
<td>22 (88)</td>
<td>18 (78)</td>
</tr>
</tbody>
</table>

Data are n (%). CR = complete response, DCR = disease control rate, ORR = objective response rate, PB = partial response, SD = stable disease, CRZ = crizotinib, All confirmed.
Background: Alectinib was approved by the FDA based on the efficacy and safety shown in two phase II studies (NP28673 [NCT01801111] and NP28761 [NCT01871805]). Clinical trial identification: NP28673 (N = 138) NP28761 (N = 87)

<table>
<thead>
<tr>
<th>Total no. of responders (no. % of pts)</th>
<th>Total no. of responders (no. % of pts by sex, N = 16)</th>
<th>Total no. of responders (no. % of pts by sex, N = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR in all responders</td>
<td>62 (44, 55)</td>
<td>20 (15, 17)</td>
</tr>
<tr>
<td>TTR in M/N pts</td>
<td>60 (44, 55)</td>
<td>20 (15, 17)</td>
</tr>
<tr>
<td>TTR in M/N pts with no prior RT</td>
<td>58 (43, 57)</td>
<td>19 (14, 19)</td>
</tr>
<tr>
<td>TTR in M/N pts with no prior RT</td>
<td>58 (43, 57)</td>
<td>19 (14, 19)</td>
</tr>
<tr>
<td>Median, wks (95% CI)</td>
<td>6.1 (5.1, 7.1)</td>
<td>4.8 (4.0, 5.7)</td>
</tr>
<tr>
<td>Median, wks (95% CI)</td>
<td>6.1 (5.1, 7.1)</td>
<td>4.8 (4.0, 5.7)</td>
</tr>
</tbody>
</table>

Results: Median follow-up was 14.5 mos (NP28673) and 9.9 mos (NP28761) (data cut-off 27 April 2015). Median TTRs and TTCRs by IBC for both studies are shown in the Table, including sub-analyses by baseline measurable (M) or non-measurable (NM) disease and no prior radiation (RT). Results were consistent between IBC and investigator assessment. In all populations, most pts who achieved a response did so by first presentation.

Conclusions: Data from the phase II alectinib studies suggest that alectinib can accrue a rapid response in patients, both systemically and in the CNS, with pts having RECIST response by first assessment in most cases. The ongoing phase III ALEX trial will assess the efficacy of first-line alectinib vs crizotinib.
Disclosure: INCa, Roche, Boeringher Ingelheim, Lilly in NSCLC management. These results can help decision maker to define conditions for better survival with limited additional costs, validating it is a cost effective alternative of simulations (more effective and less costly).

The intervention was not only cost-effective but also strongly dominant in more than 40% years saved (LYS) compared with standard care. In matched analyses, the ICER (€8,308 per life year saved (LYS)) was $4,821 per LYS. Probabilistic sensitivity analyses showed that the intervention was not only cost-effective but also strongly dominant in more than 40% of simulations (more effective and less costly).

Conclusions: Targetable GAs, including MET exon 14 alterations, were found in a majority of LSC patients, some of which occur at greater frequency than that observed in non-LSC NSCLCs. An important portion of LSC cases had high TMB, which has been associated with increased likelihood of response to immunotherapy. Thus, CGP can lead to selection of appropriate targeted therapies in this population of patients, which has historically been poorly characterized and difficult to treat.

Legal entity responsible for the study: Foundation Medicine

Funding: Foundation Medicine

Disclosure: G.M. Frampton, J. Suh, J.S. Ross, P.I. Stephens, V.A. Miller, S.M. Ali, A.B. Schrock: is an employee and has stock ownership in Foundation Medicine. S-H.I. Ou has received honoraria as an advisory board and speaker bureau member for Boehringer Ingelheim. All other authors have declared no conflicts of interest.

Lung sarcomatoid carcinoma (LSC) harbors targetable genomic aberrations and high mutational burden as observed by comprehensive genomic profiling (CGP)

Background: Knowledge of molecular status improves the clinical benefit of targeted therapy. ALK rearrangement and EGFR/KRAS mutation are the main biomarkers tested to deliver or not targeted therapies in advanced NSCLC, but their economic impact has not been studied in large prospective cohorts. One objective of the IFT-COST-PREDICT.annm study was to evaluate the incremental cost-effectiveness ratio (ICER) of a strategy including the knowledge of at least one biomarker status at first- or second-line and the most appropriate treatment (intervention strategy) compared with the standard of care without biomarker testing (reference strategy).

Methods: A cost-effectiveness analysis was performed based on prospective individual data from 802 previously never treated French patients with advanced stage of NSCLC included between 01/2013 and 02/2014 in the IFT-COST-PREDICT.annm study. Overall survival (OS) during both first- and second-line and direct medical costs related to treatment, inpatient care and biomarker testing from the French payer perspective were valued. A propensity score matching was performed to compare patients with same baseline characteristics (n=308). Probabilistic sensitivity analyses were performed to test the robustness of the results.

Results: A total of 647 patients received the intervention strategy. The incremental OS in the intervention strategy group was 6 months (p<0.001). Mean costs were €17,633 and €13,516 for the intervention and reference strategies. The ICER was €8,808 per life years saved (LYS) compared with standard care. In matched analyses, the ICER decreased to €4,821 per LYS. Probabilistic sensitivity analyses showed that the intervention was not only cost-effective but also strongly dominant in more than 40% of simulations (more effective and less costly).

Conclusions: Molecular testing before first- or second-line treatment initiation resulting in better survival with limited additional costs, validating it is a cost effective alternative in NSCLC management. These results can help decision maker to define conditions for better survival with limited additional costs, validating it is a cost effective alternative of simulations (more effective and less costly).

Legal entity responsible for the study: N/A

Funding: INCa, Roche, Boeringher Ingelheim, Lilly

Disclosure: All authors have declared no conflicts of interest.

Lung cancer (QC) A comprehensive analysis of potentially targetable genetic aberrations and clinical findings in 821 patients with squamous-cell NSCLC – a comparison of NGM and TCGA LUSC data

Background: Knowledge of molecular status improves the clinical benefit of targeted therapy. ALK rearrangement and EGFR/KRAS mutation are the main biomarkers tested to deliver or not targeted therapies in advanced NSCLC, but their economic impact has not been studied in large prospective cohorts. One objective of the IFT-COST-PREDICT.annm study was to evaluate the incremental cost-effectiveness ratio (ICER) of a strategy including the knowledge of at least one biomarker status at first- or second-line and the most appropriate treatment (intervention strategy) compared with the standard of care without biomarker testing (reference strategy).

Methods: A cost-effectiveness analysis was performed based on prospective individual data from 802 previously never treated French patients with advanced stage of NSCLC included between 01/2013 and 02/2014 in the IFT-COST-PREDICT.annm study. Overall survival (OS) during both first- and second-line and direct medical costs related to treatment, inpatient care and biomarker testing from the French payer perspective were valued. A propensity score matching was performed to compare patients with same baseline characteristics (n=308). Probabilistic sensitivity analyses were performed to test the robustness of the results.

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Conclusions: Molecular testing before first- or second-line treatment initiation resulting in better survival with limited additional costs, validating it is a cost effective alternative in NSCLC management. These results can help decision maker to define conditions for better survival with limited additional costs, validating it is a cost effective alternative of simulations (more effective and less costly).

Legal entity responsible for the study: N/A

Funding: INCa, Roche, Boeringher Ingelheim, Lilly

Disclosure: All authors have declared no conflicts of interest.
Background: Kinase gene fusions, such as ALK, ROS1 and RET fusions, are critical druggable targets for lung cancer, and the development of multiplexed testing for these fusions as well as gene mutations and amplifications is required in clinical settings. We evaluated the detectability of gene fusions by a next generation sequencing (NGS) system, which has been applied in our nationwide genomic screening project (LC-SCRUM-Japan) with academic-industrial collaboration since March 2015.

Methods: DNA and RNA extracted from lung cancer samples were subjected to a NGS system, Oncomine Comprehensive Assay, which is an amplicon-based sequencing and enables the simultaneous analysis of >4000 different genomic variants including 183 types of gene fusions. ROS1 and RET fusions were also analyzed using RT-PCR and detected fusions were confirmed by FISH.

Results: As of April 2016, 1,118 patients from 209 institutions across Japan had been enrolled in this project. Among 989 available samples, including 996 nonsmall cell carcinomas and 89 small cell carcinomas, gene fusions were detected in 83 samples (8%). The detected fusion genes were 34 ROS1 (3%), 25 RET (3%), 19 ALK (2%), 2 FGFR2 (0.2%) and 1 FGFR3 (0.1%). The concordance rates between NGS and RT-PCR for the detection of ROS1 and RET fusions were both 0.99, and the detection sensitivities/specificities of these two fusions in NGS assay were 0.94/1.00 and 0.95/1.00, respectively.

Conclusions: Our nation-wide large scale screening revealed that this amplicon-based NGS assay allows for the detection of various druggable gene fusions, especially ROS1 and RET fusions with high sensitivities and specificities, indicating that this NGS assay is clinically applicable to a molecular diagnostics for targeted therapies in lung cancer.

Legal entity responsible for the study: National Cancer Center

Funding: Japan Agency for Medical Research and Development (AMED)
Methods: Patients received durvalumab 10 mg/kg IV Q2W for up to 12 months or until unacceptable toxicity or disease progression. Safety was evaluated (CTCAE v4.03) through 90 days after last dose; confirmed response (RECIST v1.1) was based on investigator assessment. Retreatment was permitted only upon progression after 12 months of therapy in patients with disease control. Tumor PD-L1 expression was assessed using the Ventana PD-L1 IHC (SP263) assay.

Results: As of 29 April 2016, 304 NSCLC patients received durvalumab; 144 (47%) had squamous histology, and 160 (53%) had non-squamous histology; median age was 65 years (range 26–87 years); ECOG performance status was 0 in 24% and 1 in 76%; and 85% were current/prior smokers. Median number of doses was 6 (range 1–27). Any-grade drug-related AEs were reported in 57% of patients, most frequently fatigue (17%), decreased appetite (9%), and diarrhea (9%). Drug-related AEs were Grade ≥3 in 10% of patients; most common were fatigue, hyponatremia, and colitis (each 1%).

Conclusion: High PD-L1 expression in lung tumors is associated with response to PD-L1-targeted treatment. Durvalumab, an anti-PD-L1 monoclonal antibody, was evaluated in patients with advanced solid tumors, including NSCLC, in a Phase 1/2 multicenter, open-label study (NCT01693562).

**Table: 1215PD**

<table>
<thead>
<tr>
<th>Efficacy measure</th>
<th>CheckMate 017 (SQ NSCLC)</th>
<th>CheckMate 057 (NSQ NSCLC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>Nivo (n = 135)</td>
<td>Doc (n = 137)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>9.2</td>
<td>6.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.62 (0.47, 0.80)</td>
<td>0.75 (0.63, 0.91)</td>
</tr>
<tr>
<td>2-y OS, %</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>PFS</td>
<td>Nivo (n = 131)</td>
<td>Doc (n = 129)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.63 (0.48, 0.83)</td>
<td>0.89 (0.75, 1.07)</td>
</tr>
<tr>
<td>2-y PFS, %</td>
<td>16</td>
<td>NC</td>
</tr>
<tr>
<td>ORR, %</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Median DOR, mo (range)</td>
<td>25.2 (9.30-30.4)</td>
<td>8.4 (1.4 – 18.0+)</td>
</tr>
<tr>
<td>Ongoing response, %</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>No. ongoing/total responders</td>
<td>10/27</td>
<td>0/12</td>
</tr>
<tr>
<td>Grade 3-4 TRAEs, %</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Safety measure</td>
<td>Nivo (n = 135)</td>
<td>Doc (n = 137)</td>
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<tr>
<td></td>
<td>1216PD</td>
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</tr>
<tr>
<td></td>
<td>Phase 1/2 study of the safety and clinical activity of durvalumab in patients with non-small cell lung cancer (NSCLC)</td>
<td></td>
</tr>
</tbody>
</table>

**Table: 1216PD**

<table>
<thead>
<tr>
<th>OS</th>
<th>PD-L1 positive (staining in ≥25% of tumor cells)</th>
<th>PD-L1 negative (staining in &lt;25% of tumor cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Confirmed ORR (CR + PR) 195 (&amp;) 9%</td>
<td>Confirmed ORR (CR + PR) 9%</td>
</tr>
<tr>
<td>Squamous</td>
<td>Any histology</td>
<td>Any histology</td>
</tr>
<tr>
<td>First-line</td>
<td>n = 154 (18-32) 27 (19-37) 21 (12-33)</td>
<td>n = 115 (3-12) 8 (2-20) 5 (1-13)</td>
</tr>
<tr>
<td>Squamous</td>
<td>n = 49 (17-43)</td>
<td>n = 9 (1) 1 (0-8)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>n = 46 (14-41)</td>
<td>n = 24 (0-21)</td>
</tr>
<tr>
<td>Second-line</td>
<td>n = 59 (22-35)</td>
<td>n = 86 (2-14)</td>
</tr>
<tr>
<td>Third-line</td>
<td>n = 52 18.7 (7.9-22.4)</td>
<td>n = 27 8.2 (4.9-15.5)</td>
</tr>
<tr>
<td>OS (95% CI), months</td>
<td>12-month OS rate</td>
<td>12-month OS rate</td>
</tr>
<tr>
<td>Squamous</td>
<td>n = 54.8 (39.6-69.4)</td>
<td>n = 38 (19.3-57.9)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>n = 66.13 (6.6-NA)</td>
<td>n = 84 (13.4-10.0)</td>
</tr>
<tr>
<td>Third-line</td>
<td>n = 51.1 (35.9-64.4)</td>
<td>n = 38.5 (25.6-48.1)</td>
</tr>
</tbody>
</table>

17 pts with unknown PD-L1 status are not included in the analysis.

Conclusions: The safety profile of durvalumab in NSCLC is manageable and consistent with previous reports. Patients with tumors defined as PD-L1 positive had improved ORR and OS.

Clinical trial identification: NCT01693562
Legal entity responsible for the study: MedImmune

Funding: MedImmune


Overall health status (HS) in patients (pts) with advanced (adv) non–squamous (NSQ) NSCLC treated with nivolumab (nivo) or docetaxel (doc) (in CheckMate 057)

M. Peck1, J.R. Brahmer2, B. Bennett3, F. Taylor4, J.R. Porr3, M. Derosa4, F. Dastani2, R. Gralla3

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Background: The CheckMate 057 randomized, open-label, phase III study evaluated the efficacy and safety of nivo vs doc in previously-treated pts with adv NSQ NSCLC. Overall survival was significantly improved in favor of nivo vs doc, with OS rates as assessed by the Lung Cancer Symptom Scale. Here we report the impact of nivo vs doc on overall quality of life (QoL). TTD = time to first deterioration.

Methods: The EuroQol-5 Dimensions visual analog scale (EQ-5D VAS) and EQ-5D utility index (UI) (scaled 0 to 100 and 0 to 1, respectively) were assessed every other cycle (Q4W) for nivo and every cycle (Q3W) for doc for the first 6 mo on treatment (tx), then every 6 wks and at 2 post-tx follow-up visits. Changes from baseline (BL) at individual assessments (asmts), a mixed-effects model (MMRM) of change from BL over all on-tx asmts, and time to first deterioration (TTD) in HS were evaluated. The minimally important difference (MID) is 7 points for the EQ-5D VAS and 0.08 for the UI.

Results: At on-tx asmts with >10 pts (through wk 78), EQ-5D VAS briefly worsened from BL in nivo pts at wk 4 (<MID) followed by improvements until wk 78; there were no statistically significant changes from BL over all on-tx asmts, and time to first deterioration (TTD) in HS were similar between arms. A significant on-tx improvement from BL in nivo pts compared to no change for doc pts in the EQ-VAS, with a significant difference between tx arms. The MMRM analysis for EQ-5D UI showed no differences from BL within or between tx arms. TTD in the EQ-5D VAS was delayed with nivo vs doc, with KM curves separating at ~4 mo (HR, 0.76; 95% CI, 0.59–0.98). TTD per the EQ-5D UI was similar between arms.

Conclusions: The EQ-VAS results from this phase III study showed that nivo pts with previously-treated adv NSQ NSCLC had improvements in on-tx HS while doc pts on-tx HS was stable. TTD in health status per the EQ-VAS was significantly longer in nivo vs doc-treated pts.

Clinical trial identification: NCT01673867

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: M. Peck: Speakers Bureau/Consulting/Advisory role for Roche, Lilly, BMS, MSD, AZ, Pfizer, BI, Celgene. J.R. Brahmer: Consulting/Advisory role for Celgene, Lilly, Merck (BMS-uncompensated) and research funding from BMS, MedImmune/AZ, Merck. B. Bennett: Employment from AZ, research funding from Adelphi Values and consulting/advisory role with Adelphi Values. F. Taylor: Research funding and Consulting/Advisory role from Adelphi Values, a consultancy paid by BMS to analyze BMS clinical trial data. J.R. Porr: Employment and stock options from BMS. H. Dastani: Employment and Stock or Other Ownership from BMS. R. Gralla: Honoraria from Merck and consulting/advisory role with BMS, Merck, Lilly, Bi. All other authors have declared no conflicts of interest.

Table: 1218PD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Japan</th>
<th>Non-Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>MST(m)</td>
<td>12.6</td>
<td>13.4</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>0.922</td>
<td>(0.789-1.079)</td>
</tr>
<tr>
<td>Interaction test P value</td>
<td>0.3374</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: S-1 is non-inferior to DOC in terms of OS, with tolerable toxicity. S-1 monotherapy is one of the treatment options for patients with previously treated NSCLC.
In the randomized phase 2/3 KEYNOTE-010 study (NCT01905657), patients with PD-L1 positive NSCLC who progressed after platinum-based chemotherapy were randomized 1:1:1 to pembrolizumab 2 or 10 mg/kg Q3W or docetaxel 75 mg/kg. HRQoL was assessed using eEORTC QLQ-C30, QLQ-LC13, and eEuroQoL-5D. Analyses included mean change from baseline to wk 12. Pembrolizumab had a smaller proportion of TR AEs than docetaxel; fatigue, insomnia, dyspnea, hemoptysis, alopecia, SAEs were common in doc patients. Nivo patients underwent more procedures (lung-related) for Gr 3/4 AEs (77 vs 6 in 017; 165 vs 29 in 057). Doc patients had generally improved metastatic NSCLC in CheckMate 017 and 057, in squamous (SQ) and non-squamous (NSQ) NSCLC, compared to doc for patients experiencing Gr 3/4 TR AEs and generally lower for Gr 2 TR AEs. Outcomes for pembrolizumab compared to doc were consistent with improvements in or less decrement of QLQ-C30 global QoL score from baseline to wk 12. Due to improved safety, nivo may bring additional benefits in terms of AE-related HCRU relative to doc. Clinical trial identification: CheckMate 017 and 057 on treatment-related (TR) adverse events (AEs) in patients with advanced NSCLC. Here, we report HRQoL findings from KEYNOTE-010.

Summary

Background: Pembrolizumab improved HRQoL and prolonged time to deterioration of lung cancer symptom scores compared with docetaxel.

Conclusions: Pembrolizumab improved HRQoL and prolonged time to deterioration of lung cancer symptom scores compared with docetaxel.

Clinical trial identification: NCT01905657

Legal entity responsible for the study: Merck & Co, Inc.

Funding: Merck & Co, Inc.
KEYNOTE-025: Phase 1b study of pembrolizumab (pembro) in Japanese patients (pts) with previously treated PD-L1+ non-small cell lung cancer (NSCLC)  


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Background: Pembrolizumab is a potent, highly selective humanized monoclonal antibody against PD-1. We present preliminary safety and efficacy results for Japanese pts in KEYNOTE-025 (NCT02007070).  

Methods: Pts had measurable disease, ECOG performance status of 0 or 1, and adequate organ function. Prior therapy with >2 platinum-doublet chemotherapy regimens was required, an appropriate tyrosine kinase inhibitor was required for pts with sensitizing EGFR mutations (mut) or ALK translocations. All pts had PD-L1+ tumors, defined as staining in ≥1% of tumor cells as determined by a clinical trial IHC assay using the 22C3 antibody. Pembrolizumab 10 mg/kg was given every 2 weeks for up to 2 years, until disease progression or unacceptable toxicity. Primary endpoints were safety, tolerability, and overall response rate (ORR) per PER-RECIST v1.1 by central review. CT images were assessed for diagnosis of interstitial lung disease (ILD) by an independent radiologist.  

Results: 38 pts were treated with pembrolizumab. Median (range) age was 66.0 (41.78) years; 68.4% were Male; 36.8% were ECOG 0; 60.3% received ≥2 prior therapies. Most common drug-related adverse events (AEs) include malaise (n = 8), diarrhea (n = 6), AST increased, decreased appetite, pruritus, rash, maculopapular rash (n = 5 each). 21.1% experienced grade 3-5 drug-related AEs. IEL was observed in 4 pts (3 grade 2, 1 grade 3). In the 37 pts with measurable disease, ORR was 18.9% (95% CI 8.0-35.2). At the time of analysis (median follow-up, 11.5 months), 85.7% responses were ongoing, and the median response duration was not reached (range, 9.1+ to 46.1+ months). In the 11 pts who had PD-L1 expression in ≥50% of tumor cells, ORR was 27.3% (95% CI 6.0-61.0). Median PFS was 4.1 months (95% CI 2.0-6.2), and 6-month PFS and 1-year overall survival (OS) rates were 38.8% and 51.0%, respectively. In the 11 pts who had PD-L1 expression in >50% of tumor cells, ORR was 27.3% (95% CI 6.0-61.0). Median PFS was 4.1 months (95% CI 1.6-6.9) and 6-month PFS and 1-year OS rates were 41.7% and 56.3%, respectively.  

Conclusions: Pembrolizumab was generally well tolerated in Japanese pts, but ILD should be carefully monitored. Pembrolizumab showed promising anti-tumor efficacy in Japanese pts with previously treated PD-L1+ NSCLC.  

Clinical trial identification: NCT02007070  

Legal entity responsible for the study: MSD K.K.  

Funding: MSD K.K.  

Disclosure: T. Kato: Research fund. MSD. T. Takahashi: Grants from MSD K.K., grants and personal fees from Eli Lilly Japan K.K., grants and personal fees from Chugai.  

Legal conflict of interest: N.  

J. Lahmari1, L. Mezoula1, M. Chantier1, J. Lahmari1, J. Remon1, M.V. Blutghen1, J. Adam1, A. Gazzah1, J. Remon1, D. Planhacard1, J-C. Soria1, C. Carmelita1, B. Besse1  

1Department of medical oncology, Gustave Roussy, Villejuif, France, 2Department of biostatistics, Gustave Roussy, Villejuif, France, 3Department of Pathology, Gustave Roussy, Villejuif, France, 4Department of Radiology, Gustave Roussy, Villejuif, France  

Background: Immune Checkpoint inhibitors (IC) represent a major step forward in treating advanced NSCLC by improving survival and clinical outcomes. In patients (pts) with non-squamous NSCLC PD-L1 negative NSCLC, IC increases the risk of early death compared to docetaxel. Risk later reversed for the two study groups to increasingly favor IC, as reflected in the eventual crossing of the Kaplan–Meier curves. Tumor Progression Rate (TPR) integrates tumoral dynamics and kinetics. Therefore, TCR gives additional information vs RECIST criterion. We hypothesized that TCR could identify a subset of pts in which IC could accelerate tumor progression, leading to early death.  

Methods: We performed a clinical and radiological retrospective case study of all NSCLC pts treated by IC in a single institution between Dec. 12 and Feb. 16. For each patient, CT scan during immunotherapy and previous treatment were centrally reviewed by a senior radiologist and assessed according to RECIST criteria. We calculated TCR at baseline of IC (baseline CTScan (n) vs n-1 CTscan) and TGR during IC (n + 2 CTScan vs n + 1 CTscan). We further estimated the difference (deltaTGR) between TGR during IC and TGR at baseline: deltaTGR = 0 means the treatment slows tumor progression whereas deltaTGR < 0 means that the treatment speeds up tumor growth.  

Results: 89 pts were eligible: 58% were male, median age 60 (41-78); 15% never smokers. 62 pts had adenocarcinoma, 21 squamous and 6 other histologies. Median follow-up was 14 pts; 35% 6-12 months, 20% ≥12 months. Median age of previous IC was 1 (1-8), median number of lines was 1 (1-2). Median number of tumors was 1 (1-3). 9.4-102.15 vs. 22.5 months [CI 95% 0-54.8] in HLA-A2 positive vs. negative patients (log-rank; p = 0.340). In univariate analysis, there was no correlation between outcome and histology. No correlation was found between outcome and lines of previous IC.  

Conclusions: Our results suggest that IC increased tumor progression in around 10% of pts and thus could illustrate a deleterious effect in this subset of pts. Further work is needed to confirm this finding and characterize this population.  

Legal entity responsible for the study: Dr Benjamin BESSE  

Funding: Gustave Roussy  

Disclosure: All authors have declared no conflicts of interest.  

HLA-A2 and immune checkpoint inhibitors in advanced non-small cell lung cancer (NSCLC) patients  

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1Medical Oncology Department, Gustave Roussy, Villejuif, France, 2Laboratory of Immunomonitoring in Oncology, UMR 7225 CNRS/Inserm, Gustave Roussy, Villejuif, France, 3Drug Development Department (DITEP), Gustave Roussy, Villejuif, France, 4Pathology Department, Gustave Roussy, Villejuif, France  

Background: The class I human leucocyte antigen (HLA) molecules play a critical role in tumor recognition by T cells and the loss of expression seems to be an escape mechanism in which IC could accelerate tumor progression, leading to early death. Immune-checkpoint inhibitors (IC) induce paradoxical tumor growth, expressed as percent increase in tumor volume per month, increased by at least 50% during IC. Clinical characteristics (age, sex, smoking status, pathology) of the 9 pts were not different from other pts.  

Methods: Advanced NSCLC patients treated with nivolumab, pembrolizumab or atezolizumab were prospectively included from Nov. 2013 to Apr. 2016 in our institute. HLA-A2 status was assessed by flow cytometry. PD-L1 was analysed by immunohistochemistry. Clinical and biological data were collected at baseline and after cycle 1. Statistical analysis was performed with SPSS v.20.  

Results: Out of 125 patients treated, HLA-A2 status was available for 30 patients. 50% were male, median age was 61 years (29-77); 86% were smokers and 83% had performance status 0-1. 18 (60%) were adenocarcinoma, 7 (23.3%) squamous and 5 (16.7%) others histologies. 2 NSCLCs were EGFRmut, 2 ALK+, 7 KRASmut. 19 patients had a deltaTGR < 0 in 79 pts and >0 in 20 pts. Among the 20 pts with deltaTGR > 0, 9 had a deltaTGR ≥ 50%, meaning that tumor growth, expressed as percent increase in tumor volume per month, increased by at least 50% during IC. Clinical characteristics (age, sex, smoking status, pathology) of the 9 pts were not different from other pts.  

Conclusions: Our preliminary results suggest that HLA-A2 status could influence the outcome in NSCLC patients treated with immune checkpoint inhibitors. An updated analysis on 59 patients will be presented.
### Cost effectiveness and estimate of economical impact of immune checkpoint inhibitors for NSCLC relative to PD-L1 expression

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1Clinical Oncology, LifeSciences - Universidade Federal de São Paulo, São Paulo, Brazil; 2Medical Oncology, Portuguese Institute of Oncology-oncologia, Porto, Portugal; 3Clinical Oncology, Honor Health, Scottsdale, AZ, USA. 

**Background:** Recent clinical trials have shown that immune checkpoint inhibitors are active against several neoplasms, including lung cancer. Tumor PD-L1 receptor expression is being studied as a predictive biomarker. The objective of our study is to assess the cost-effectiveness and economical impact of nivolumab and pembrolizumab with or without the use of PD-L1 as a biomarker.

**Methods:** We developed a decision-analytic model to determine the cost-effectiveness of PD-L1 assessment and second-line treatment with NIVO or PEMBRO versus docetaxel. The model used outcomes data from randomized clinical trials and drug acquisition costs from the United States. We also included the costs of adverse events and post-progression therapies. Published utility values were used. Health effects were expressed as quality-adjusted life-years (QALY) and incremental cost-effectiveness ratios (ICER) were calculated. Furthermore, we used US and Brazilian epidemiological data to estimate the economical impact of the treatment with or without the use of PD-L1 as a biomarker.

**Results:** We included 3 RCTs (2 with NIVO and 1 with PEMBRO). Among all patients with squamous histology, the incremental QALY of NIVO was 0.23. The ICER was US$ 128 K. PD-L1 expression improved incremental QALY only for patients with PD-L1 > 5% and > 10% (by 15% and 18% respectively). Among all patients with non-squamous histology, the incremental QALY of NIVO was 0.12. The ICER was US$ 121 K. PD-L1 expression improved incremental QALY for patients with PD-L1 > 1%, > 5% and > 10% (by 6%, 15% and 137%, respectively). All patients treated with PEMBRO had 1% of PD-L1 expression; the incremental QALY was 0.13. The ICER was US$ 116 K. PD-L1 expression above 5% improved QALY by 18%. The estimated cost of treating all American patients with NIVO in the second-line was $1.57 billion yearly. The estimate of expenses treating only patients with PD-L1 > 1% with PEMBRO was $0.97 billion yearly.

**Conclusions:** The use of PD-L1 expression as a biomarker increases cost-effectiveness and decreases the economical treatment burden with immune checkpoint inhibitors.

**Legal entity responsible for the study:** Universidade Federal de São Paulo

**Funding:** The authors

**Disclosure:** All authors have declared no conflicts of interest.

#### Preliminary efficacy and safety data of nivolumab in never smoker patients with advanced squamous NSCLC: Experience from Italian sites participating in the Expanded Access Programme (EAP)


**Background:** Among NSCLC patients who received third-line therapy, we examined the association of PD-L1 expression and EGFR mutations with survival.

**Methods:** Third-line therapy NSCLC patients diagnosed during 2001-2012 were selected from the Danish Lung Cancer Group Registry. We retrieved patient data from population-based medical registries, and paraffin-embedded tumor tissue from pathology archives. We assessed PD-L1 expression using the Ventana IHC (SP263) validated assay (using 25% cutoff for high versus low), and genotyped EGFR to identify mutations. Exon 19 (G796A, G796V, G796R, G796D, and G796S); Exon 20 (S768I, T790M, and insertions), and Exon 21 (L858R, L858Q, L858F, and L858H) via a PCR-based kit. Follow-up was from third-line therapy start to the first of death, emigration, or 31/12/2014. We used Cox regression to compute hazard ratios (HR) and associated 95% confidence intervals (95% CI) for PD-L1 and EGFR.

**Results:** Among 344 third-line therapy patients, 185 (54%) were men, 165 (48%) were aged >60 years of diagnosis, and the majority were ever-smokers. 200 (58%) had adenocarcinoma histology, 89 (25%) had high PD-L1 expression in their tumors and 27 (8%) had EGFR mutations. Compared to patients with wildtype EGFR tumors, those with EGFR mutations less often showed high PD-L1 expression (21%, 95% CI = 4%, 38% versus 25%, 95%CI = 19%, 31%), Fisher’s exact p-value = 0.81. Median overall survival differed little by PD-L1 status, but was longer in patients with mutant compared with wildtype EGFR. Neither PD-L1 expression nor EGFR mutations were significantly associated with survival.

**Table:**

<table>
<thead>
<tr>
<th>PD-L1</th>
<th>No. of deaths</th>
<th>Median Survival (months) (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>249</td>
<td>208</td>
<td>8.0 (6.9, 9.1)</td>
</tr>
<tr>
<td>High</td>
<td>85</td>
<td>72</td>
<td>8.3 (6.1, 11.6)</td>
</tr>
<tr>
<td>EGFR</td>
<td>Mutant</td>
<td>260</td>
<td>213</td>
</tr>
<tr>
<td>Wildtype</td>
<td>27</td>
<td>22</td>
<td>11.0 (9.9, 12.1)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, histology (adenocarcinoma versus other)
Conclusions: Our findings suggest no association of PD-L1 expression or EGFR mutations with survival in third-line therapy NSCLC patients.

Clinical trial identification: Not applicable

Legal entity responsible for the study: N/A

Funding: AstraZeneca

Disclosure: T. Dalvi: TD is an employee and shareholder of MedImmune/AstraZeneca. E. Heddeman. Funding to support this work from AstraZeneca Inc., Gaithersburg, MD 20878. A. Midra, N. Shir, R. Brody, D. Lawrence, D. Potter, J. Walker: Employee and shareholder of AstraZeneca. J. Fryzek: JPP was employed by AstraZeneca 2009–2011. JPP received funding to support this work from AstraZeneca Inc., Gaithersburg, MD 20878. J. Rigas: Consultant physician to AstraZeneca. A. Mellemgaard: Honoraria and/or travel expenses from Lilly, Boehringer Ingelheim, BMS, MSD, S. Hamilton-Dutoit. Research funding from AstraZeneca. Honoraria or consulting Agen. H.T. Swenson: Research funding from Epipstat. All other authors have declared no conflicts of interest.

Impact of severe adverse events during second-line therapy on healthcare costs in patients with advanced non-small cell lung cancer (aNSCLC)

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Background: Elderly with aNSCLC represents a population at higher risk of severe adverse events (AEs) due to poorer performance status and more comorbidities than younger patients (pts). Severe AEs may also impose a financial burden on the healthcare system. In a cohort of elderly pts with aNSCLC who received second-line therapy (2L), we assessed the impact of severe AEs on healthcare costs.

Methods: The SEER-Medicare database was used to identify pts with aNSCLC aged ≥65 years diagnosed between 2007-11 who initiated 2L up to end of Medicare data availability of 12/31/2013. Pts were divided into 2 cohorts of with and without severe AEs during time on 2L therapy. 57 AEs were pre-specified based on literature review and oncologist consensus. Severe AEs were defined as AEs requiring a hospitalization. The incremental impact of severe AEs on all-cause healthcare costs incurred during 2L was estimated using two-part regression models adjusted for age, sex, region, stage at diagnosis (dx), and overall disease burden at 2L start.

Results: Of 3,967 pts who initiated 2L, 1,624 (41%) had ≥1 severe AE. Use of chemotherapy only or targeted therapy-based regimens were comparable between pts without severe AEs during the period between the aNSCLC dx and 2L initiation (anemia 69% vs 60%; weight loss 27% vs 20%; renal failure 15% vs 11%; congestive heart failure 25% vs 17%; bleeding 35% vs 31%, all p < .05). Total costs for pts with severe AEs were more than double that of pts without severe AEs (Table), with most of the difference due to inpatient costs.

Table: 1227P

<table>
<thead>
<tr>
<th>AE cause occurred on 2L</th>
<th>Mean cost per pt per month of 2L (2014 USD)</th>
<th>Adjusted difference (*significant at p &lt; .05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with severe AEs N = 1,624</td>
<td>Pts without severe AEs N = 2,343</td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td>$16,135</td>
<td>$7,559</td>
</tr>
<tr>
<td>Medical service costs</td>
<td>$14,350</td>
<td>$6,158</td>
</tr>
<tr>
<td>Cancer†</td>
<td>$4,118</td>
<td>$4,468</td>
</tr>
<tr>
<td>Non-cancer tx†</td>
<td>$10,433</td>
<td>$1,691</td>
</tr>
<tr>
<td>Emergency room</td>
<td>$114</td>
<td>$60</td>
</tr>
<tr>
<td>Inpatient</td>
<td>$3.99</td>
<td>$7.47</td>
</tr>
<tr>
<td>Outpatient</td>
<td>$422</td>
<td>$473</td>
</tr>
<tr>
<td>Home care</td>
<td>$3.37</td>
<td>$160</td>
</tr>
<tr>
<td>Hospice</td>
<td>$371</td>
<td>$104</td>
</tr>
<tr>
<td>Skilled nursing facility</td>
<td>$456</td>
<td>$32</td>
</tr>
<tr>
<td>Durable medical equipment</td>
<td>$143</td>
<td>$90</td>
</tr>
<tr>
<td>Other medical services</td>
<td>$702</td>
<td>$693</td>
</tr>
<tr>
<td>Pharmacy costs</td>
<td>$1,285</td>
<td>$1,401</td>
</tr>
</tbody>
</table>

1. Chemotherapy, targeted therapy, radiation therapy or supportive care therapy (i.e., growth factors, anticoagulants, antibiotics and corticosteroids), includes both the cost of the drugs (where applicable) and provider fees for treatment administration.

Efficacy and safety data from patients with advanced squamous NSCLC and brain metastases participating in the nivolumab Expanded Access Programme (EAP) in Italy

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Background: Brain metastases are a very common secondary localization of disease in patients (pts) with lung cancer. The prognosis of these pts is still poor and they are usually excluded from clinical trials. The EAP provided an opportunity to evaluate the feasibility of nivolumab treatment in this patient population outside of a controlled clinical trial in Italy.

Methods: Nivolumab was available upon physician request for pts aged ≥18 years with a diagnosis of squamous non-small cell lung cancer (Sq-SqCLC) who had relapsed after a minimum of one prior systemic treatment for stage IIIIB/stage IV Sq-NSCLC. Pts included in the analysis had received ≥1 dose of nivolumab and were monitored for adverse events using Common Terminology Criteria for Adverse Events. Nivolumab 3 mg/kg is administered intravenously every 2 weeks to a maximum of 24 months. Pts in the analysis included had received ≥1 dose of nivolumab and were monitored for adverse events using Common Terminology Criteria for Adverse Events.

Results: Of 372 patients with Sq-NSCLC participating in the EAP in Italy, 38 (10.2%) had asymptomatic and controlled brain metastases. With a median number of doses 6 (range, 1–18) and a median follow-up of 4.5 months, the disease control rate was 47.3%, comprising 1 pt with a complete response, 6 patients with a partial response and 11 with stable disease. Four pts were treated beyond RECIST defined progression. As of April 2016, median progression-free survival and overall survival among patients with brain metastases were 5.5 months and 6.5 months, respectively. Among 38 pts, 21 pts (55.3%) discontinued treatment for any reason except toxicity; 1 out of 38 discontinued due to AE (2.6%).

Conclusions: These preliminary data show efficacy of nivolumab in patients with Sq-NSCLC with brain metastases, with safety results consistent to what already reported in previous studies, thus encouraging the use of nivolumab in this population with poor prognosis.

Legal entity responsible for the study: ASST Monza

Funding: IMS

Disclosure: F. Grossi: Present on advisory board. All other authors have declared no conflicts of interest.
First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy in lung adenocarcinoma patients with EGFR mutation (CONVINCE)

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Background: We assessed icotinib as first-line therapy compared with pemetrexed/ cisplatin plus pemetrexed maintenance in advanced lung adenocarcinoma patients with sensitizing EGFR mutation.

Methods: This phase 3, open-label, randomized study (CONVINCE) was conducted at 18 sites in China. Eligible patients (pathologically confirmed lung adenocarcinoma, 19. 21 EGFR mutation-positive [m+], treatment naive) were 1:1 randomized to receive icotinib (125 mg three times daily) or pemetrexed (500 mg/m2, day 1) plus cisplatin (75 mg/m2, day 1) every 21 days, non-progressive patients after 4-cycle chemotherapy continue to receive maintenance until disease progression or intolerable toxicity. Randomization was stratified by performance status, smoking status, and disease progression. Cox-regression models were used to compare survivals.

Results: 669 patients were screened (January 2013 to August 2014), in which 268 were enrolled and randomized (148 for each group), and 285 were patients (icotinib: 148, chemotherapy: 137). Patients’ characteristics were well balanced between groups. Icotinib significantly improved PFS (9.9 months [95% CI 8.5-11.2] vs 7.3 months [6.0-8.0], HR 0.65, 95% CI 0.48-0.88, p = 0.004) compared with the chemotherapy group. Subgroup analyses showed the PFS benefit for icotinib persisted among most clinically relevant subgroups (gender, performance status, smoking status, and disease stage), especially in patients harboring EGFR L858R mutation (11.2 months [95% CI 9.2-13.5]) vs 7.3 months [5.7-8.4]; p = 0.001). Significantly fewer adverse events (AEs) and treatment-related AEs were seen in the icotinib group (AEs: 78.4% vs 94.2%, p < 0.001; TRAEs: 50.7% vs 89.1%, p < 0.001). The most common adverse events were cough (17.6%), rash/acne (15.5%), and elevated AST (10.1%) for icotinib and nausea (28.1%) and vomiting (11.8%) for pemetrexed. The most common grade 3/4 AEs were anemia (16.3%) for icotinib and neutropenia (10.0%) for pemetrexed.

Conclusions: First-line icotinib offers superior efficacy compared with cisplatin/ pemetrexed plus pemetrexed maintenance therapy in advanced lung adenocarcinoma patients with sensitizing EGFR mutation.

Clinical trial identification: ClinicalTrials.Gov NCT01719536.

Legal entity responsible for the study: Betta Pharmaceuticals Co., Ltd.

Funding: Betta Pharmaceuticals Co., Ltd.

Disclosure: L. Ding: Salaried, F. Tan: Salaried employee and stock owner of Betta Pharmaceuticals Co., Ltd. All other authors have declared no conflicts of interest.

Efficacy of first-generation EGFR-TKIs on patients with NSCLC harboring EGFR uncommon mutations: a pooled analysis

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Department of Thoracic Oncology, The 1st Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

Background: NSCLC Patients with common sensitive EGFR mutations (deletion in exon 19 or L858R mutation in exon 21) benefit remarkably from first-generation EGFR-TKIs (gefitinib and erlotinib). In this meta-analysis, we aim to investigate their treatment efficacy in patients with uncommon EGFR mutations (5768, L861Q, G719X, R705K, etc.) by comparing with that in patients with common mutations.

Methods: We searched PubMed for eligible studies from the date of inception to 31st December, 2015. Overall objective response rate (ORR) and 6-month progression free survival (PFS) rates were estimated by fixed-effect model and relative effects were presented using odds ratio (OR). Mutations within the same exons were grouped in the subgroup analyses.

Results: Of 6404 patients from 13 included studies, 466 (7.3%) patients were diagnosed as EGFR uncommon mutations and chose gefitinib and erlotinib as any line of treatment. In single-arm synthesis, the overall ORR in uncommon and common mutations was 34.0% (95% CI 22.5 to 45.7) and 71% (66.7 to 75.3), respectively. Direct comparison indicated significantly lower response in uncommon-mutation patients (OR = 0.30, 95% CI 0.23 to 0.41, P < 0.001). Patients with uncommon mutations, compared with common ones, were associated with an inferior 6-month PFS rate (OR = 0.44, 95% CI 0.32 to 0.59, P < 0.001).

In individual case analysis, ORR was 50.7% (16.3 to 75.0), 33.3% (N.A.), 32.1% (13.2 to 51.0) and 38.5% (19.5 to 57.6) in patients with rare mutations in EGFR exon 19, 18, 20 and 21 exons, respectively. In patients with complex mutations (two or more uncommon mutation sites), the ORR was 64.2% (49.9 to 78.5).

Conclusions: Compared with those in sensitive mutations, first-generation EGFR-TKIs presented less clinical benefits in uncommon mutations, but the responses are still considerable, historically compared with that of chemotherapy, especially in complex mutations. First-generation EGFR-TKIs remained an option for uncommon mutations but decision-making should be cautious. Exact efficacy in each specific mutation site merits future studies with larger sample size.

Legal entity responsible for the study: N/A

Funding: The first affiliated hospital of Guangzhou medical university

Disclosure: All authors have declared no conflicts of interest.

OSI407

P6S non-disruptive mutation is a negative predictive factor in EGFR M+ NSCLC treated with TKI

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Background: P53 mutations are common in lung cancer, and have also been described in EGFR mutated patients. The impact of p53 mutations in EGFR M+ patients is controversial, especially if classified as disruptive and non-disruptive according to their complexity. The impact of p53 mutations in EGFR M+ patients is still not clear.

Methods: EGFR M+ patients were treated with TKI. The impact of p53 mutations (mutant vs wild type) was assessed in a pooled analysis of clinical trials.

Results: 490 patients from a single center diagnosed with lung cancer stage IV were studied for the presence of EGFR as well as inactivating p53 mutations. Methods for the detection of EGFR M+ included Sanger Sequencing and hybridization based COBAS testing, hybrid cage next generation sequencing. P53 mutations were detected by Sanger Sequencing and either MiSeq or hybrid cage NGS. Clinical characteristics of patients with p53 disruptive and non-disruptive mutation were compared using chi-square test. The impact of p53 mutations on treatment outcome was assessed by univariate and multivariate analysis.

Conclusions: P53 disruptive and non-disruptive mutations are differentiated. P53 should be tested prospectively in EGFR-M+ patients as management of patients on 1st line TKI may be different.

Legal entity responsible for the study: Prof. Dr. Frank Griesinger

Funding: Pius Hospital Oldenburg, University Oldenburg

Disclosure: All authors have declared no conflicts of interest.

OSI408

Osimertinib in EGFR T790M positive advanced NSCLC (aNSCLC) – real-life data from the French temporary authorization for use (ATU) program

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Background: Osimertinib, an oral, irreversible EGFR-TKI selective for sensitizing (EGFRm) and T790M resistance mutations, has been shown to be effective and well tolerated in clinical studies for pts with EGFR T790M positive aNSCLC. Pts in France had early access to osimertinib through an ATU program before approval.

Methods: Pts with EGFR T790M positive aNSCLC were eligible if they had received prior EGFR-TKI therapy and a platinum-based chemotherapy (CT) or had CT
N.Varoqueaux:OtherfromAstraZeneca,duringtheconductofthestudy;grants,personalfeesand
non-financialsupportfromMsd,BMS,Roche,Lilly,BI,Amgensexclusive.
Allotherauthorshavedeclarednocausesofinterest.

**Disclosure:**

Allauthorshavedeclarednoconflictofinterest.

**Background:**

RecentfindingssuggestthatafractionofEGFRmutantNSCLCcarries
additionaldriverswhichcouldpotentiallyaffecttheactivityofEGFRTKIs.
WeinvestigatedtheroleofKRAS,Nras,BRAF,PIK3CA,METandERBB2mutations
(othermutations)ontheoutcomeofNSCLCptswithEGFRmutantEGFR
mutations,suggestingintra-tumorheterogeneity.A790Mmutationwasalso
foundin9132tumorsamples(6.8%).Theprogressionfreesurvival(PFS)ofpts
withoutothermutationswas11.3monthsversus7monthsinptswithothermutations
(Log-rank

**Results:**

132pts,treatedbetweenJun2008andDec2014in7centers,werenrolled.
medianage71(range41-92);70%women;61%neversmokers.AnalysisofEGFR
mutantNSCLCsampleswithNGSreveals aspirationofhotspotmutationsingenethan
theEGFR,includingKRAS,Nras,BRAF,PIK3CA,METandERBB2.

**Conclusions:**

ThesefindingssuggestthatablogroupofEGFRmutanttumorthave
intra-tumorheterogeneityandthatthisphenomenonmightaffecttheactivityoffirst
eGFRTKIs.

**Clinicaltrialidentification:**

ThisobservationalstudiesabasedontheEthical
CommitteeofthePascaleInstitute:protocoln.16/14COS

**Legalentityresponsibleforthestudy:**

IstitutoNazionaleTumori“Fondazione
G.Pascale”-IRCNS,Naples,Italy

**Funding:**AssociazioneItalianaperlaRicercaCanceroin

**Disclosure:**Allauthorshavedeclarednoconflictofinterest.

**Tumorheterogeneityaffectstheactivityofepidermalgrowth
factorreceptor(EGFR)tyrosinekinaseinhibitors(TKIs)inEGFR
mutantnon-smallcelllungcancer(NSCLC)patients(pts)**

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E.Crocechi5,A.Morabito2,A.Montanino3,G.Rocco2,D.Galetta5,E.
S.Montagna2,L.Cristi2,V.Ludoviti3,B.Vincenzi3,E.Barletta3,C.Pintu3,
F.Ferraro2,G.Botti5,M.C.Piscitello5,F.Parella2

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FondazionePascale,Naples,Italy,**
**ClinicalTrialUnit,IstitutoNazionaleTumori—IRCNS:Fondazione
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AsofMarch2016,350ptswere treated,14excluded (prescriberdecision/patientdeath).
36pts(10.3%)experiencedwithdrawalfordiseaseprogression.Investigatorreportedsafety
(data=350)showed36pts(10.3%)experiencedtreatment-relatedAE,13pts(3.7%)hadAEsleading
to discontinuation.12pts(3.4%)died(1deathrelatedattributedbyinvestigator).9pts
(2.6%)hadAEsresultingindose reductions;3pts(0.9%)hadtreatment-relatedAEs.

**Conclusions:**InptswithEGFR790MpositiveaNSCLC,osimertinibhadantitumour
activitywithasimilarORRtothatinsurgicalstudies,withgoodtolerability.
Identificationofeligibletipsisfeasibleindailypatientsatcancerprogressionby
T790MtestingonrebiopsyorusingctDNA.

**Clinicaltrialsituation:**NL4606-4609September2015

**Legalentityresponsibleforthestudy:**AstraZeneca

**Funding:**AstraZeneca

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Novartis,SanoAveti,BMS,Roche,Lilly,Pfizer,andgrantsfromNovartis.
P.M. Péró:Personal fees from Astra-Zeneca, Clavis Oncology, Roche, Boehringer-Ingelheim,
outside the submitted work. A. Cortot: Personal fees from Asta-Zeneca. J. Cadranel:
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All other authors have declared no conflicts of interest.

**Disclosure:**Allauthorshavedeclarednoconflictofinterest.

**Background:**AnafitinipNPUprogramstartedin2010afterthePhase2b/3
LUX-Lung1trialsdemonstratedsignificantlyimprovedprogression-freesurvivaland
objective response rate (ORR) with atezolizumab versus placebo in advanced NSCLC patients following failure of EGFR and 1–2 lines of chemotherapy. Methods: Eligible advanced NSCLC patients had either progressed after clinical benefit on prior EGFR and/or had an activating EGFR/HER2 mutation; had exhausted all other treatments, and were ineligible for clinical trials. Time to treatment failure (TTF) was defined as the time from drug start to the date of treatment discontinuation. Results: Data as of January 2016 from 3966 NSCLC patients from 41 countries (6 continents) are reported here. Patients were heavily pretreated, with approximately 50% receiving 4 or more lines of therapy. Among 2645 patients with known tumour EGFR status, 92.8% were EGFR mutation-positive. Median TTF for atezolizumab was calculated for 2862/3966 patients (72.2%) based on available data. TTF was 4.4 months for all patients, similar to the TTF for patients reported as EGFR mutation-positive, or as harbouring common or uncommon EGFR mutations (each 4.3 months). For patients with response assessments reported (n = 1141/2862, 39.8%), the ORR was 23% (271/1141) for all patients and 25% (181/725) for those with NSCLC harbouring any EGFR mutation. Notably, a 26% (26/100) ORR was reported in patients with NSCLC harbouring uncommon EGFR mutations, including 19% (11/58) in T790M mutation-positive patients and 35% (7/20) in those with insertions in exon 20. No new/unexpected safety findings were observed. Conclusions: This atezolizumab NPU program in ~4000 NSCLC patients who were refractory to several therapies, including prior EGFR, revealed encouraging TTF durations and ORR. The atezolizumab safety profile was as anticipated.

Clinical trial registration: N/A

Legal entity responsible for the study: Boehringer Ingelheim

Funding: Boehringer Ingelheim

Disclosure: F. Capuzzo: Membership on advisory board or board of directors (Roche, AstraZeneca, BMS, Pfizer). R. Soo: Membership on advisory board or board of directors (AstraZeneca, Boehringer Ingelheim, Lilly, Merck, Novartis, Pfizer, Roche). M. Schuler: Membership on advisory board/board of directors (AZ, BI, BMS, Celgene, IQWig, Lilly, Novartis), corporate-sponsored research (BI, BMS, Novartis). G. Allen: Membership on advisory board/board of directors (AZ, BI, Celgene, GSK, Lilly, Novartis), patients (University Duisburg-Essen). T.S.K. Mok: Stock (Sanomics Ltd); advisory board (Adro; Roche/ Genentech, Pfizer, Eli Lilly, BI, Merck Serono, MSD, Janssen, Cleon Oncology, BioMarin, GSK, Novartis, SPI Pharmaceutical, ACEA Biosciences, Inc., Vertex Pharmaceuticals, Ayes & Bodeus, BMS, geneDeco Co. Ltd, Oncogenex Technologies Inc.); board of directors (IASCCL, Chinese Lung Cancer Research Foundation Ltd, CSO, HKCTC); corporate-sponsored research (AZ, BI, Pfizer, Novartis, SFI, Roche, MSD, Cleon Oncology, BMS). G. Stehle: Employment and patent/royalty/other intellectual property (Boehringer Ingelheim). A. Cseh: Employment (Boehringer Ingelheim); stock (MEDIA). R.M. Lorenzo: Employment and consulting/advisory role (Boehringer Ingelheim). S. Linden (Employment (Boehringer Ingelheim). N.D. Forman: Employment (Boehringer Ingelheim); stock/other ownership (INSYS Therapeutics). C.-M. Tsai: Honoraria (Pfizer, Roche, Eli Lily, Boehringer Ingelheim, AstraZeneca). All other authors have declared no conflicts of interest.

Correlation between programmed death-ligand 1 (PD-L1) expression and T790M status in EGFR-mutant non-small cell lung cancer (NSCLC)

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Background: Correlation between PD-L1 expression and T790M status is unclear. Therapeutic interventions could affect PD-L1 expression, and rebiopsied fresh samples may be desirable to analyze PD-L1 expression.

Methods: We retrospectively analyzed PD-L1 expression and T790M status in rebiopsied samples of EGFR-mutant NSCLC after acquired resistance. PD-L1 immunohistochemistry was performed using the SP 142 anti-PD-L1 antibody for tumor cell membrane staining. H-score was adopted to evaluate both percentage and intensity, and scores ≥ 1 were defined as PD-L1+ , and scores ≥ 10 as strong PD-L1+. T790M status was examined using the PNA-LNA PCR clamp or cycleave method. Results: We investigated 63 available rebiopsied histologic samples in 45 patients. Median H-score in T790M+ (n = 25) samples was 0 (range, 0–6), whereas T790M− (n = 38) was 1 (range, 0–91) (Wilcoxon, p = 0.0453). PD-L1+ was confirmed in 12 (48%) of 25 T790M+ samples, and in 28 (74%) of 38 T790M− (p = 0.0383). Strong PD-L1+ was identified in 0 (0%) T790M+ , but in 3 (8%) T790M− (p = 0.150). Ten patients received multiple rebiopsies. In 7 of these 10 patients, T790M status had changed from T790M+ to T790M−. Among 4 of these 7 PD-L1 expression also changed from PD-L1− to PD-L1+ , in accordance with T790M status from T790M+ to T790M−. Median overall survival (OS) of PD-L1+ (n = 30) vs. PD-L1− (n = 15) were 55.0 months vs. not reached months, respectively (p = 0.0171). Median OS of T790M+ (n = 16) vs. T790M− (n = 29) was 80.3 vs. 55.0 months, respectively (p = 0.1340).

Conclusions: T790M+ status was correlated to lower PD-L1 expression. Conversely, T790M− status was associated with higher PD-L1 expression, suggesting a potential efficacy of anti-PD-1/PD-L1 immunotherapies for T790M− population. PD-L1 expression might have a prognostic value, even in EGFR-mutant NSCLC.

Legal entity responsible for the study: Boehringer Ingelheim

Funding: Foundation for Biomedical Research and Innovation

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Rociletinib-associated cataracts in EGFR-mutant NSCLC

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Afinatin efficacy and cerebrospinal fluid concentration in NSCLC patients with EGFR mutation developing leptomeningeal carcinomatosis

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Background: Afinatin (AFA) is an effective treatment in advanced non-small-cell lung cancer (NSCLC) patients harboring epidermal growth factor receptor (EGFR) mutation. However, there are few reports about the cerebrospinal fluid (CSF) penetration rate and the efficacy for treatment of central nervous system (CNS) metastasis. Therefore, we conducted a study to evaluate the CSF penetration rate and efficacy of AFA in NSCLC patients harboring EGFR mutation with leptomeningeal carcinomatosis (LC).

Methods: Eligibility criteria included performance status (PS) 0-3, aged 20 years or older, pathologically proven NSCLC, harboring EGFR mutation, with LC, adequate organ function, and written informed consent. Patients received AFA (40mg/kg every day), and the blood and CSF level of AFA was measured before administration of AFA on the eighth day. The primary endpoint was the CSF penetration rate. Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety profile.

Results: A total of 11 patients were enrolled. And we could analyze the blood level in 10 patients and the CSF level in 8 patients. Median patient age was 66 years. All patients had advanced adenocarcinoma. In EGFR mutation status, 5 patients had exon 19 deletion, 3 had L858R and 3 had exon (exon18) mutation. There were 3 patients of PS2 and 4 patients were PS3. Almost all patients received AFA after third-line or further line chemotherapy. The median blood level was the 88.2 (range: 30.4-97.8) ng/ml, the median CSF level was 1.4 (range: 0.39-2.85) ng/ml and the median CSF penetration rate was 1.65 (range: 0.1-0.25%). The ORR was 27.3%. Median OS was 3.8 (95%CI 1.1-13.1) months and median PFS was 2.0 (95%CI 0.6-5.8) months. Hematological toxicity was mild, however diarrhea and skin toxicities were relatively strong, especially in patients with poor PS.

Conclusions: The median CSF penetration rate of AFA was higher than the rate in previous reports, however the rate was lower compared with that of erlotinib in the prior reports. The efficacy for LC was moderate. And we have to take care of diarrhea and skin toxicities, especially in the patients with poor PS.

Clinical trial identification: UMIN000014065

Legal entity responsible for the study: Shin-ichi Atagi

Funding: Kinki-Chuo Chest Medical Center


Progression of leptomeningeal metastases in advanced EGFR-mutated non-small cell lung cancer

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Background: Leptomeningeal metastasis (LM) has become increasingly common in patients with advanced EGFR-mutated non-small cell lung cancer (NSCLC) treated with epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), but data are incomplete with respect to clinical features and treatment outcomes of LM in this population.

Methods: We retrospectively evaluated 420 advanced NSCLC patients effectively treated with EGFR-TKI. We studied LM progression of those patients, defining this as newly developed leptomeningeal metastases after a response to EGFR-TKI with or without pre-existing brain parenchyma lesions.

Results: Among 420 patients, LM occurred in 29 (6.9%). Patients with EGFR L858R mutations were more likely to experience LM than those with exon 19 deletions (P < 0.006). The median time to LM progression was 16.5 months (95% CI 11.9-20.8). The prognosis for LM patients was poor and the median survival was 5.2 months (95% CI 3.2-7.2) after LM diagnosis. Patients who received RSC are significantly shorter than those with anti-tumor treatment (1.9m vs 6.0m, P < 0.001). Patients who received whole brain radiotherapy (WBRT) had significantly longer survival time compared with who did not (6.0m vs 3.9m, P = 0.038). And there are significant difference between patients with performance status ≤2 and >2 (14.2m vs 2.3m, P = 0.001). However, no statistical difference were found between patients switched to erlotinib and those who did not after LM (P = 0.941). similar trends were observed in the subset analysis in patients with stop or continue taking gefitinib (P = 0.330).

Conclusions: For advanced EGFR-mutated NSCLC patients who were effectively treated with EGFR-TKI, L858R mutation might be associated with higher risk of LM progression compared with exon 19 deletion. Performance status was an important prognostic factor. WBRT was a rational choice of the appropriate therapy and can improve the outcomes after LM progression.

Legal entity responsible for the study: Yongmei Liu

Funding: Natural Science Foundation of China (No. 81472196)

Disclosure: All authors have declared no conflicts of interest.

Predictive factors for T790M mutation in plasma in patients after progression to 1st line tyrosine-kinase inhibitor (TKI) with or without subsequent lines of TKI or chemotherapy for metastatic epidermal growth factor mutator (EGFR)-mutated non-small-cell lung cancer (NSCLC)


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Background: Liquid re-biopsy has become an acceptable alternative to tumor re-biopsy to identify acquired T790M mutation after tyrosine-kinase inhibitors with or without subsequent chemotherapy for metastatic EGFR-mutated NSCLC. We prospectively investigated if there were any predictors for development of acquired T790M mutation in plasma DNA.

Methods: Patients with tumour-biopsy proven activating EGFR mutations who received 1st line TKI with or without subsequent lines of TKI and/or chemotherapy after failure to 1st line TKI were prospectively recruited. Blood (10ml EDTA) was taken for plasma DNA for the detection of T790M mutation at the time of progressive disease to TKI with or without subsequent TKI/chemotherapy. Univariable and multivariable logistic regression was performed for clinical and molecular predictors for presence of T790M mutation.

Results: 68 patients received TKI alone with or without further TKI/chemotherapy before liquid re-biopsy at the time of progressive disease. 19 (21.4%) patients with initial exon 19 deletion versus 8 (23.8%) patients with initial exon 21 mutation developed T790M on liquid re-biopsy (p = 0.332). Univariable analysis showed that age ≥75 years (OR 4.15, 95% CI 1.06-16.21, p = 0.041), ≥2 sites of distant metastases before 1st line TKI (OR 13.51, 95% CI 6.65-111.1, p = 0.015) and exon 19 deletion (vs. exon 21 mutations) (OR 3.04, 95% CI 1.08-9.51, p = 0.035) were significant predictive factors, while multivariable analysis showed that ≥2 sites of distant metastases (OR 13.70, 95% CI 1.64-111.1, p = 0.001) and exon 19 deletion (OR 3.09, 95% CI 1.03-9.29, p = 0.039) were independent predictive factors of development of T790M mutation.

Conclusion: Use of chemotherapy and use of more than 1 line of TKI were not predictors.

Disclosure: All authors have declared no conflicts of interest.
Similar to afatinib data in Caucasian pts. Funding: AstraZeneca.

**Results:** Of 361 pts recruited across 104 sites in France (116 incident pts), 283 were EGFR mutation-positive and received 1st line gefitinib (94 incident pts). EGFR mutation subtypes data were available for 260 (82 incident pts). Median duration of follow-up: 20.8 months. In the total 1st line population: median age was 71 years, 61% were never-smokers, 73% had performance status 0-1 and 33% had brain metastases. ORR was 68.5% (95% CI 61.9, 72.9), median PFS was 11.5 months (95% CI 10.0, 13.4) and median OS from initiation of gefitinib was 25.7 months (95% CI 23.4, 27.9). Better outcomes were observed with exon 19 Del vs L858R mutations (Table), especially in incident pts.

**Conclusions:** EPIDIAUER provided a large cohort of French pts with EGFR mutation-positive NSCLC treated with 1st line gefitinib. Higher ORR and prolonged OS/PFS in exon 19 Del vs L858R mutations indicate that this subtype represents distinct tumours which may be more sensitive to EGFR TKI therapy. Findings were similar to afatinib data in Caucasian pts. Funding: AstraZeneca.

**Legal entity responsible for the study:** AstraZeneca

**Funding:** AstraZeneca

**Disclosure:** M. Perol, F.-J. Moret, J. Cadralen: Honoraria received from AstraZeneca (Advisory Board). M. Licour: Employee of AstraZeneca. All other authors have declared no conflicts of interest.

### Table 1244P

<table>
<thead>
<tr>
<th>EGFR mutation subtype, n (%)</th>
<th>Total pts (n = 260)</th>
<th>Incident pts (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%) (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39 (83) (72.3, 66.0)</td>
<td>102 (78)</td>
<td>26 (63)</td>
</tr>
<tr>
<td>18.1) (70.8, 73.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS, median months (95% CI)</td>
<td>12.2 (9.1, 18.1)</td>
<td>6.4 (5.3, 7.7)</td>
</tr>
<tr>
<td>OS, median months (95% CI)</td>
<td>27.2 (24.0, 34.6)</td>
<td>18.1 (10.9, 26.4)</td>
</tr>
</tbody>
</table>

CI, confidence interval; EGFR, epidermal growth factor receptor; NC, non-calculable; OS, overall survival; PFS, progression-free survival

**Background:** In the absence of randomized data comparing osimertinib to platinum-based doublet chemotherapy (PBDC) in patients (pts) with metastatic EGFR mutation-positive NSCLC (NGCL) who have progressed after EGFR-TKI, an adjusted indirect comparison can offer a robust estimate of treatment effect. The IMPRESS study placebo arm (PBDC) (data cut-off [DCO] 2014 May) included a subgroup of pts with the T790M mutation and disease progression following response to EGFR-TKI. Pts had similar demographic and disease characteristics as those in AURA extension (NCT01802632) and AURA2 (NCT02092431) trials of osimertinib (DOO May 2015), and therefore represent a valid comparator to demonstrate differences in outcomes.

**Methods:** The efficacy of osimertinib relative to PBDC was assessed using an adjusted indirect comparison of two non-randomized data sets comprising pts with a confirmed T790M mutation (by tissue or plasma DNA) respectively and AURA (N = 403) and IMPRESS placebo arm (N = 60). A propensity score (PS) approach was used to adjust for differences in baseline demographics and disease characteristics. Baseline characteristics of both groups were compared using statistical tests. The PS model included 22 variables with P < 0.2. Only pts within the PS distributions of both treatment groups were included in the final analyses. To adjust for remaining differences between the groups, PS was incorporated as a covariate in the treatment comparison of osimertinib relative to PBDC for each endpoint.

**Results:** Following estimation of PS for each pt and balancing across the groups (osimertinib N = 287, PBDC N = 51) osimertinib demonstrated: A statistically significant improvement in median progression-free survival (PFS) of 9.7 months vs 5.3 months (HR 0.28, 95% CI 0.19–0.42, P < 0.0001). An improvement in objective response rate (ORR) of 64.6% vs 34.8% (OR 4.76, 95% CI 2.21–10.26, P < 0.001). An improvement in objective response rate (ORR) of 64.6% vs 34.8% (OR 4.76, 95% CI 2.21–10.26, P < 0.001). An improvement in objective response rate (ORR) of 64.6% vs 34.8% (OR 4.76, 95% CI 2.21–10.26, P < 0.001). An improvement in objective response rate (ORR) of 64.6% vs 34.8% (OR 4.76, 95% CI 2.21–10.26, P < 0.001). An improvement in objective response rate (ORR) of 64.6% vs 34.8% (OR 4.76, 95% CI 2.21–10.26, P < 0.001). An improvement in objective response rate (ORR) of 64.6% vs 34.8% (OR 4.76, 95% CI 2.21–10.26, P < 0.001).

**Conclusions:** In this indirect comparison, a statistically significant improvement in PFS and ORR was demonstrated for osimertinib compared to PBDC. AURA3 will provide a randomized comparison of osimertinib and PBDC.

**Legal entity responsible for the study:** AstraZeneca

**Funding:** AstraZeneca

**Disclosure:** F. Andersohn: Consultancy fees from AstraZeneca. H. Mann, C. Hoyle: AstraZeneca employee and stock in AstraZeneca. T. Mitsuomi: Membership on advisory boards for AstraZeneca, Chugai, Boehringer Ingelheim, Roche and Pfizer. Corporate-sponsored research for Boehringer Ingelheim, Chugai and Pfizer. No stock ownership or other substantive relationships. T.S.K. Mok: Advisory boards: AZ, Roche, Pfizer, Eli Lilly, Bi, MerckSerono, MSD. Janssen, Clovis, Bio Marin, GSK, Novartis, SFI.
Discordance of EGFR mutation status between primary lung adenocarcinomas and corresponding metastatic tumors and the sensitivity to EGFR tyrosine kinase inhibitors

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Background: A considerable proportion of non-small cell lung cancer has shown a discrepancy in epidermal growth factor receptor (EGFR) mutations between matched primary and metastatic tumors. The aim of this study was to clarify the distribution of EGFR mutations in primary lung adenocarcinomas and corresponding metastatic tumors with highly sensitive method of detecting EGFR mutations and to identify a better predictive marker of the response to EGFR tyrosine kinase inhibitors.

Methods: We performed peptide nucleic acid-mediated real-time polymerase chain reaction clamping to identify EGFR mutations in paired primary lung adenocarcinomas and metastatic tumors in 24 patients who were treated with EGFR tyrosine kinase inhibitors, but had not received EGFR tyrosine kinase inhibitors before both primary and metastatic tissues were sampled.

Results: EGFR mutations were detected in 20 primary lung adenocarcinomas (83.3%) and in 19 corresponding metastatic tumors (79.2%). EGFR mutations showed a discordance rate of 20.8% (5 of 24 patients) between primary lung adenocarcinomas and corresponding metastatic tumors. Three patients with EGFR-mutated primary tumors lost their mutations in the metastatic tumors and showed no response to EGFR tyrosine kinase inhibitors. Two patients had EGFR mutations in the metastatic tumors but not in the primary lung adenocarcinomas and experienced a partial response to EGFR tyrosine kinase inhibitors.

Conclusions: EGFR mutations were discordant between matched primary and metastatic tumors before EGFR tyrosine kinase inhibitor therapy in a significant portion of lung adenocarcinomas. Our findings suggest that the EGFR mutation status of metastatic tumors in patients with metastatic lung adenocarcinoma is a predictive marker of the response to EGFR tyrosine kinase inhibitors. EGFR tyrosine kinase inhibitors are used to treat metastatic disease, therefore, a more aggressive pursuit of tissue sampling from metastatic lesions may be indicated to accurately determine EGFR mutations for planning of the use of EGFR tyrosine kinase inhibitors to treat metastatic lung adenocarcinoma.

Legal entity responsible for the study: Singapore General Hospital

Funding: Singapore General Hospital

Disclosure: All authors have declared no conflicts of interest.

Frequency of driver mutations in EGFR wt NSCLC using mass spectrometry: Experience of Area Vasta Romagna

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Background: Targeted therapy of advanced non-small cell lung cancer (NSCLC) has changed the outcome of patients with specific gene alterations. In particular, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors have improved the outcome of patients with EGFR-mutated lung adenocarcinoma (AC). We analyzed the frequency of other potentially targetable driver mutations in a series of advanced EGFR-wild type (wt) NSCLC patients.

Discordance of EGFR mutation status between primary lung adenocarcinomas and corresponding metastatic tumors and the sensitivity to EGFR tyrosine kinase inhibitors

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Background: A considerable proportion of non-small cell lung cancer has shown a discrepancy in epidermal growth factor receptor (EGFR) mutations between matched primary and metastatic tumors. The aim of this study was to clarify the distribution of EGFR mutations in primary lung adenocarcinomas and corresponding metastatic tumors with highly sensitive method of detecting EGFR mutations and to identify a better predictive marker of the response to EGFR tyrosine kinase inhibitors.

Methods: We performed peptide nucleic acid-mediated real-time polymerase chain reaction clamping to identify EGFR mutations in paired primary lung adenocarcinomas and metastatic tumors in 24 patients who were treated with EGFR tyrosine kinase inhibitors, but had not received EGFR tyrosine kinase inhibitors before both primary and metastatic tissues were sampled.

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Legal entity responsible for the study: Singapore General Hospital

Funding: Singapore General Hospital

Disclosure: All authors have declared no conflicts of interest.

Detection of EGFR T790M resistance mutation: real-time allele-specific PCR versus Sanger sequencing

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Background: Lung cancer is the most common cause of death from cancer worldwide, and 85-90% of lung cancers are non-small cell lung cancer (NSCLC). Presence of driver mutations in epidermal growth cell receptor (EGFR) gene in a subset of NSCLC has led to the use of tyrosine kinase inhibitors (TKI) that inhibit the EGFR signalling pathway. Tumours which harbour certain EGFR mutations may exhibit initial response to EGFR-TKIs, but many will develop resistance mutations post-treatment, commonly at amino acid position 790 (T790M) of exon 20. Never EGFR inhibitors with activity against T790M-mutated NSCLC have recently been made available. Accurate detection of T790M in patients whose disease progressed on initial TKI therapy is thus vital for subsequent management. Here, we evaluated the performance of Sanger sequencing in detecting T790M mutation against a real-time allele-specific PCR.

Methods: Ninety-six FFPE samples sent to our laboratory for T790M mutation detection by cobas® EGFR Mutation test (Roche), between July 2014 and March 2016 were included in this study. Archived extracts were used for Sanger sequencing of EGFR exon 20 using an in-house developed protocol.

Results: T790M was detected in 49.5% (47/98) and 47.9% (46/98) of the samples by the cobas® assay and Sanger sequencing respectively. Taking cobas® assay as the gold standard for 95% with valid real-time PCR results, Sanger sequencing yielded a sensitivity of 95.7% (45/47) and specificity of 100% (48/48). Of the 3 discordant results, cobas® assay detected T790M in 2 samples (both with tumour contents <30%) not detectable by Sanger sequencing, while Sanger sequencing detected T790M in one sample which repeatedly yielded an inconclusive result for exon 20 on the cobas® assay. Overall, concordance rate between the two methods was 96.9% (93/96).

Conclusions: Sanger sequencing was generally comparable to, but slightly less sensitive than real-time PCR in detecting T790M. Sanger sequencing may be useful in the event of inconclusive results by the real-time assay. Otherwise, for post-treatment T790M mutation testing, where initial driver mutations had already been identified, Sanger sequencing, which requires samples with higher tumour content, offers little advantage over real-time PCR.

Legal entity responsible for the study: Singapore General Hospital

Funding: Singapore General Hospital

Disclosure: All authors have declared no conflicts of interest.
Methods: 461 advanced EGFR-wt NSCLC patients enrolled from Area Vasta Romagna between January 2013 to December 2014 were included in the study: KRAS, BRAF, ERBB2, PIK3CA, NRAS, ALK, MAP2K1, RET and DDR2 mutations were analyzed by Myriad® Lung Status kit (Dartech Pharmacogenetics) on MiSeq® Mass Spectrometry (massARRAY®, AGENA BIOSCIENCE). ERBB4 was evaluated by direct sequencing and EML4-ALK and ROS1 rearrangements were assessed by immunohistochemistry or fluorescence in situ hybridization.

Results: 217 (47%) patients showed at least one alteration. In particular, 71%, 6.5%, 2.7%, 1.8%, 1.4% and 1.4% patients had mutations in KRAS, BRAF, PIK3CA, NRAS, ERBB2 and MAP2K1 genes, respectively. Only one (0.5%) patient showed a mutation in ERBB4 gene. EML4-ALK and ROS1 rearrangements were observed in 10.6% and 4.1% patients, respectively. The clinical characteristics of mutated patients are reported in Table 1. Overlapping mutations were observed in 5 (2.3%) KRAS-mutated patients, one (0.5%) was in PIK3CA, 3 (0.6%) showed an EML4-ALK translocation and one (0.5%) patient showed both BRAF and PIK3CA alterations. Correlation analyses between the different mutations and patient outcome are ongoing. Table

Conclusions: Driver mutations were detected in about 58% of EGFR-wt lung ADC patients. Such alterations could represent potential targets for therapy and could be evaluated in routine multiplexed testing to obtain a wider tumor molecular characterization.

EGFR mutation in squamous cell carcinoma of lung - Does it carry the same connotation as in adenocarcinomas?

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Background: EGFR Tyrosine Kinase Inhibitors (TKIs) have greatly improved outcomes of EGFR mutation positive Adenocarcinomas of lung. In contrast, the significance of EGFR mutation in metastatic Squamous Cell Carcinoma (SCC) of Lung has been debated. We looked at the outcomes of EGFR mutation positive SCC of Lung treated at our centre.

Methods: All patients with metastatic NSCLC treated at our centre from 2010 to 2015 were included in the analysis. EGFR kinase domain mutations were determined in all patients with metastatic NSCLC using Taqman based real time PCR. Treatment decisions including the decision to start TKI and the type of TKI (erlotinib or gefitinib) were at the discretion of the treating physicians. Response assessment was done according to RECIST 1.1. Progression free survival (PFS) was calculated from date of start of TKI till progression or last follow up. Overall Survival (OS) was calculated from date of first consultation to date of death or last follow up.

Results: EGFR mutation was detected in 29 patients. Median age of the patients was 59 years with 22 males and 7 females. 19 out of the 29 patients received TKIs at some point of time during their treatment course and 7 patients having received frontline TKI therapy. Response assessment for patients receiving TKI showed partial response in 5 out of 19 patients, stable disease in 4 out of 19 patients and progression in 3 patients. Formal response assessment was not available for 6 patients. The median PFS of patients treated with TKIs was 5.0 months. The median OS of the whole EGFR positive SCC cohort was 6.6 months. On univariate analysis, patients having received TKI was the only factor associated with a significantly better median OS of 13.48 months vs 2.58 months (p = 0.008). Patients with exon 19 mutation tended to have better overall survival (p = 0.059). On multivariate analysis using Cox Regression Analysis, patients receiving TKI therapy, EGOCG performance status <2, Esmo 19 mutation and non-smoking status were associated with significantly better OS.

Conclusions: EGFR mutation in SCC of lung predicts better outcome if given TKI but it may be inferior to the outcomes seen in adenocarcinoma patients.

Legal entity responsible for the study: Tata Memorial hospital

Funding: Self funded

Disclosure: All authors have declared no conflicts of interest.

Addressing disease progression in EGFRm+ NSCLC patients

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Background: Although EGFR-Tyrosine Kinase Inhibitors (TKIs) have improved disease management in EGFR mutation-positive NSCLC patients, all patients experience disease progression (PD) and ultimately die. In current practice, EGFR-TKIs are often continued beyond PD (REc1ST1.1), however optimal management at PD remains ambiguous. We set out to study the survival differences and patient characteristics associated with continuation vs discontinuation of EGFR-TKI at PD retrospectively at a single institution: the Tom Baker Cancer Centre, AB (Canada 2010–2014).

Methods: EGFRm+ NSCLC patients treated with an EGFR-TKI were retrospectively analyzed. Demographic and clinical data, EGFR mutation type, treatment-variants at PD (chemotherapy, radiation, continuation with EGFR-TKI) were collected. SPSS-v19 was used to generate Kaplan–Meier survival curves. Progression-free survival (PFS) (time from initiating EGFR-TKI to PD) and time-to-complete EGFR-TKI-cessation (time from initiating EGFR-TKI to cessation of TKI completely, if extended beyond PD), were assessed.

Results: 127 EGFRm+ NSCLC patients received EGFR-TKIs. 106/127 (83%) developed PD (RECIST 1.1) (64.8% F35.2 M, 95% adenocarcinoma, smoking history: 47%; ex 19 del/L858R/other: 45.7%/35.4%/18.9%). Median PFS was 7.9 months, while median overall survival (mOS) was 17.3 months. A log rank test showed a statistical significant difference in mOS between exon 19 deletion and L858R (22.6months vs 13.6months, 95% CI, 14.8 to 21.9, P-value = 0.014). At PD, 54.7% continued EGFR-TKI treatment. 42% received other forms of treatments. Female gender, PD with solitary-lessions and younger age are associated with EGFR-TKI continuation at PD.

Conclusions: This study confirms the difference in survival of ex 19 del vs L858R patients when treated with an EGFR-TKI. Additionally, it is common practice for oncologists to continue TKI treatment beyond PD. Further analysis, by time-to-complete EGFR-TKI cessation, will provide a more stratified base for future clinical-trials exploring treatment at EGFR-TKI-PD.

Legal entity responsible for the study: University of Calgary

Funding: AstraZeneca

Disclosure: All authors have declared no conflicts of interest.

A prospective study of epidermal growth factor receptor tyrosine kinase inhibitors concurrent with radiotherapy for non-small-cell lung cancer patients with bone metastasis

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Background: To establish the safety profile and efficacy of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) concurrent with radiotherapy (RT) in patients with non-small-cell lung cancer (NSCLC) who have only bone oligometastases (1-3 lesions) progression after EGFR-TKIs therapy.

Methods: Between June 2012 and January 2015, 28 patients with Stage IV NSCLC were enrolled in this prospective study. They were treated with EGF-TKIs (gefitinib 250mg or erlotinib 150 mg, oral daily), and concurrent with bone metastasis RT with curative intent when these patients had only bone oligometastases (1-3 lesions) progression. The RT plans were individually designed on the basis of tumor size and normal tissue volume constraints. The RT plans have two styles: 30Gy/10f. All patients were available for assessment of toxicity and efficacy. The primary endpoints were acute toxicity and overall survival. The secondary endpoints included median survival time and progression-free survival (PFS).

Results: All patients completed the treatment protocol. Acute skin, hematologic, esophageal, gastrointestinal and systemic toxicities were mild. No serious adverse reaction was noting. With a median follow up of 21.5 months, the local control rate of 92.8% was achieved for the bone metastases lesions. Median PFS, median survival time were 16.2, and 21.5 months, respectively. The 1- and 2-year PFS rates were 69.8% and 26.2%, and 1-, 2-, and 3-year overall survival rates were 77.9%, 46.8%, and 23.4%, respectively.
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Background: Brain metastases (BMs) are a frequent complication of non-small-cell lung cancer (NSCLC). Whole brain radiation therapy (WBRT) is a standard treatment for BMs, but favorable response of BMs with mutant epidermal growth factor receptor (EGFR) against tyrosine kinase inhibitors (TKIs) have also been reported. The aim of this study is to clarify the effect of TKIs alone without radiation therapy for BMs from EGFR-mutant NSCLC.

Methods: BMs from NSCLC with EGFR-mutation were enrolled. Gefitinib was administrated first, and erlotinib or afatinib was used at tumor progression. Erlotinib (or afatinib) was also selected for patients whose BMs had developed after gefitinib (or erlotinib). The primary endpoint was overall survival after BM (OS), and the secondary endpoints were maximum response to TKIs, time to progression of intracranial lesions, and time to salvage radiation therapy (RT).

Results: In this study, 108 patients with BMs were enrolled. The types of mutations were as follows: exon 19 deletion in 62, exon 28 1285R in 39, and other types of mutations in 7 cases. During the follow-up period, 70 deaths were observed but only 17 of these deaths were owing to the progression of intracranial lesions. The medium OS was 20.9 months. The response rates of first-line and second-line TKIs were 76.9% and 70.6%, respectively. The medium time to progression of intracranial lesions was 14.5 months, and medium time to salvage RT was 19.9 months. Among the patients, gefitinib was administrated in 83 (first-line) and erlotinib in 59 (first-line, second-line). The response rates of gefitinib and erlotinib were 76.8% and 78.6%, and the time to progression of intracranial lesions after gefitinib and erlotinib were 13.9 and 20.3 months, respectively. We could not find any significantly different response of BMs to TKIs owing to the types of mutations.

Conclusions: TKIs showed favorable control of BMs harboring EGFR-mutation without RT. At progression, other types of TKIs still showed excellent effect. TKI first treatment could postpone RT, and feasible for BMs from EGFR-mutant NSCLC.

Legal entity responsible for the study: Chiba Cancer Center

Funding: JSPS KAKENHI grant

Disclosure: All authors have declared no conflicts of interest.

1255P

Next generation sequencing identifies actionable mutations in EGFR-wild type and KRAS mutant non-small cell lung cancer patients

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Background: Identification of actionable mutations in patients’ tumors is essential in guiding therapy. The aims of this study were: a) to validate mutation detection by next-generation sequencing (NGS) in a cohort of NSCLC patients and b) to identify molecular subgroups within EGFR wild-type and KRAS mutant NSCLCs.

Methods: We used the Ion Torrent AmpliSeq Colon and Lung cancer panel to analyze formalin-fixed paraffin-embedded tumors from 76 NSCLC patients previously tested for EGFR mutations by Sanger Sequencing. The sensitivity of the method was assessed by using commercial reference FFPE standards with defined allelic frequencies. DNA was isolated from microdissected tumor tissue and sequencing was performed in the Ion PGM platform.

Results: Tumors were sequenced to a median coverage of 650x. The sensitivity of mutation detection was estimated at 4% and for mutation reporting we have used a baseline prevalence of 2.5%. Precision of the method was demonstrated by analyzing four tumor specimens two times in different library preparations and runs. A complete concordance was observed between the previously defined Sanger genotyping and the corresponding variants detected using NGS. A single mutation was detected in 30 of 76 (39.5%) specimens, two in an additional 30 (39.5%) whereas mutations in more than two genes were detected in 11 (14.5%). The most frequently mutated genes were TP53 (41/76; 54%) and KRAS (23/76; 30%). Among KRAS mutated tumors, 3 (13%) carried STK11, 2 (8.7%) kinase inactivating BRAF mutations and one (4.4%) the BRAF V600E. Between the EGFR/KRAS wild type tumors, 3 (11%) had a mutation in the PI3K pathway, 3 (7.3%) carried mutations in MET, 2 (4.9%) had the BRAF V600E and 6 (14.6%) carried STK11 loss of function mutations.

Conclusions: NGS can be used for molecular diagnostics in NSCLC and may detect additional mutated pathways that can be targeted using novel therapies.

Legal entity responsible for the study: Medical School, University of Crete

Funding: University of Crete

Disclosure: All authors have declared no conflicts of interest.

1256P

Hypomagnesaemia and its management following treatment with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs): Results from 3 randomized studies of neucitumumab (NECI) plus chemotherapy in first-line treatment of patients with stage IV non-small cell lung cancer (NSCLC)

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Background: Hypomagnesaemia is a known side effect of certain chemotherapies and an established class effect of EGFR mAbs. We present analyses of hypomagnesaemia and its management from 3 clinical trials of NECI, a human IgG1 anti-EGFR mAb recently approved in the US and the EU for the treatment of advanced squamous NSCLC.

Methods: Three randomized global trials of 1st-line treatment for stage IV NSCLC were included in this analysis. SQUIRE (N = 1079) and INSPIRE (N = 616) were phase 3 trials of gemcitabine (Gem)-cisplatin (Cis) +/- NECI in squamous NSCLC and pemetrexed (Pem)-Cis +/- NECI in non-squamous NSCLC, respectively. JFCL (N = 161) was a phase 2 trial of paclitaxel (Pac)-carboplatin (Carbo) +/- NECI in squamous NSCLC. Per protocols, hypomagnesaemia was managed by investigators based on local guidelines. Hypomagnesaemia frequency was assessed based on reported adverse events (AEs) and lab data.

Results: Hypomagnesaemia was reported as an AE more frequently in the NECI arms as compared to the control arms. SQUIRE: NECI + Gem-Cis 31.2% (9.3% grade ≥3) vs. Gem-Cis 15.7% (1.6%). INSPIRE: NECI + Pem-Cis 26.6% (7.6%) vs. Pem-Cis 12.8% (2.2%). JFCL: NECI + Pac-Carbo 24.3% (5.7%) vs. Pac-Carbo 12.7% (0%). Hypomagnesaemia rates based on lab values were higher as compared to reported AEs across trials and in both arms. A small number of patients discontinued treatment due to hypomagnesaemia (0.6% SQUIRE, 0% INSPIRE and JFCL). In SQUIRE, no clear association was seen between hypomagnesaemia and hypokalemia or cardiac events. Magnesium levels gradually reduced over time and stabilization of magnesium supplementation was given to 31% and 16.7% of patients with hypomagnesaemia based on lab data for NECI + Gem-Cis and Gem-Cis, respectively.

Conclusions: Hypomagnesaemia is a common side effect of the combinations of chemotherapy with NECI, especially Ca-containing regimens. Our data suggest that hypomagnesaemia may be underreported and perhaps undertreated. Close monitoring of magnesium levels and prompt repletion is recommended.

Clinical trial identification: NCT00981058, NCT00982111, NCT01769391

Legal entity responsible for the study: Eli Lilly and Company

**Background:** Pts aged 2–18 years were eligible if they had locally advanced/metastatic NSCLC, ECOG PS 0–1, EGFR mutation confirmed by Terascreen EGFR RQG PCR (Qiagen), and c-Met positivity determined by IHC using CONFIRM anti-c-Met mAb (SP44; Ventana/Roche). A 3+3 design was used with expansion at the RP2D. Pts received tepotinib 300 or 500 mg/day plus gefitinib 250 mg/day (T300G250) or 500 mg/day (T500G250). The primary endpoint was to determine the RP2D of tepotinib plus gefitinib; secondary objectives included pharmacokinetics (PK), safety, and antitumor activity.

**Results:** 18 pts were enrolled (median age 65 [41–78], male 8). Pts had received a median of 2 (1–8) prior regimens including an EGFRi. 6 received T300G250, 12 T500G250. Non-cancer-limiting toxicities were observed, and tepotinib ≤500 mg/day was confirmed as the RP2D. T500G250 was associated with treatment-related grade 3–4 increased amylase (n = 2), increased lipase (2), neutropenia (1) and hyperglycemia (1). No evidence of cumulative toxicity was noted. The best overall response was partial response in 5/18 pts, 4 with IHC 2+ tumors treated with T300G250 and 1 with an IHC 2+ tumor (T300G250). 4/18 pts had stable disease (SD) (3 IHC 2+ [1 T300G250, 2 T500G250], 1 IHC 3+ [T500G250]). PK were expected based on historical comparisons.

**Conclusions:** Tepotinib was well tolerated in combination with gefitinib; the RP2D of tepotinib in combination with gefitinib in NSCLC is 500 mg/kg/day. Data show evidence of antitumor activity, with responses mainly in pts with c-Met IHC 3+ tumors and SD in pts with IHC 2+ tumors. A phase II trial is randomizing 4–136 pts with T790M/c-met+ tumors who have failed first-line tepotinib to gefitinib or cisplatin/pemetrexed.

**Clinical trial identification:** NCT01982955

Legal entity responsible for the study: Global Clinical Development Center Merck Serono (Beijing) Pharmaceutical R&D Co., Ltd

**Funding:** Merck KGaA

**Disclosure:** Y-L. Wu: Honoraria in the past two years from Roche, AstraZeneca, Eli Lilly, Sanofi. Research for Roche, AstraZeneca, Eli Lilly, Pfizer, Merck Serono, Novartis, BMS, ACEA Biosciences. R. Soo: Paid honoraria and consulted for AstraZeneca, Boehringer Ingelheim, Lilly, Merck, Novartis, Pfizer, Roche. Conducted research for AstraZeneca, Pfizer, Roche, Taiho, Merck Serono, Novartis, Servier Bayer. J. Yang: Honoraria from AstraZeneca, Roche, Eli Lilly, Boehringer Ingelheim, Pfizer. Paid consultant to AstraZeneca, Roche/Genentech, Eli Lilly, Boehringer, Clovis, Novartis, Bayer, MSD, Merck, Pfizer, Astellas, Daichi-Sankyo, Celgene. Funded research Boehringer. U. Stammberger: Employee of Merck KGaA. W. Chen, G. Locatelli: Employee of Merck. K. Park: Advisory role for Astra Zeneca, Boehringer Ingelheim, Clovis, Eli Lilly, Hanu, ORO, Roche, in the past 2 years. Research for AstraZeneca. All other authors have declared no conflicts of interest.

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**1256P**

**Tepotinib plus gefitinib in patients with c-Met-positive/ EGFR-mutant NSCLC: Recommended phase II dose (RP2D), tolerability, and efficacy**


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**Background:** Patients (pts) with NSCLC treated with EGFR inhibitors (EGFRi) ultimately develop resistance, often through c-Met activation. Dual EGFR and c-Met inhibition is therefore a rational option to treat c-Met+, EGFR-resistant NSCLC. Tepotinib is a highly selective c-Met inhibitor with good tolerability and promising efficacy against solid tumors. This phase I/II trial, conducted in Asia, examined tepotinib plus gefitinib in pts with c-Met+/EGFR-mutant NSCLC.

**Methods:** Pts aged ≥18 years were eligible if they had locally advanced/metastatic NSCLC, ECOG PS 0–1, EGFR mutation confirmed by Terascreen EGFR RQG PCR (Qiagen), and c-Met positivity determined by IHC using CONFIRM anti-c-Met mAb (SP44; Ventana/Roche). A 3+3 design was used with expansion at the RP2D. Pts received tepotinib 300 or 500 mg/day plus gefitinib 250 mg/day (T300G250 or T500G250). The primary objective was to determine the RP2D of tepotinib plus gefitinib; secondary objectives included pharmacokinetics (PK), safety, and antitumor activity.

**Results:** 18 pts were enrolled (median age 65 [41–78], 8 male). Pts had received a median of 2 (1–8) prior regimens including an EGFRi. 6 received T300G250, 12 T500G250. Non-cancer-limiting toxicities were observed, and tepotinib ≤500 mg/day was confirmed as the RP2D. T500G250 was associated with treatment-related grade 3–4 increased amylase (n = 2), increased lipase (2), neutropenia (1) and hyperglycemia (1). No evidence of cumulative toxicity was noted. The best overall response was partial response in 5/18 pts, 4 with IHC 2+ tumors treated with T300G250 and 1 with an IHC 2+ tumor (T300G250). 4/18 pts had stable disease (SD) (3 IHC 2+ [1 T300G250, 2 T500G250], 1 IHC 3+ [T500G250]). PK were expected based on historical comparisons.

**Conclusions:** Tepotinib was well tolerated in combination with gefitinib; the RP2D of tepotinib in combination with gefitinib in NSCLC is 500 mg/kg/day. Data show evidence of antitumor activity, with responses mainly in pts with c-Met IHC 3+ tumors and SD in pts with IHC 2+ tumors. A phase II trial is randomizing 4–136 pts with T790M/c-Met+ tumors who have failed first-line tepotinib to gefitinib or cisplatin/pemetrexed.

**Clinical trial identification:** NCT01982955

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**Funding:** Merck KGaA

**Disclosure:** Y-L. Wu: Honoraria in the past two years from Roche, AstraZeneca, Eli Lilly, Sanofi. Research for Roche, AstraZeneca, Eli Lilly, Pfizer, Merck Serono, Novartis, BMS, ACEA Biosciences. R. Soo: Paid honoraria and consulted for AstraZeneca, Boehringer Ingelheim, Lilly, Merck, Novartis, Pfizer, Roche. Conducted research for AstraZeneca, Pfizer, Roche, Taiho, Merck Serono, Novartis, Servier Bayer. J. Yang: Honoraria from AstraZeneca, Roche, Eli Lilly, Boehringer Ingelheim, Pfizer. Paid consultant to AstraZeneca, Roche/Genentech, Eli Lilly, Boehringer, Clovis, Novartis, Bayer, MSD, Merck, Pfizer, Astellas, Daichi-Sankyo, Celgene. Funded research Boehringer. U. Stammberger: Employee of Merck KGaA. W. Chen, G. Locatelli: Employee of Merck. K. Park: Advisory role for Astra Zeneca, Boehringer Ingelheim, Clovis, Eli Lilly, Hanu, ORO, Roche, in the past 2 years. Research for AstraZeneca. All other authors have declared no conflicts of interest.
Safety of necitumumab and pembrolizumab combination therapy in patients with stage IV non-small cell lung cancer (NSCLC): a phase 1b expansion cohort study


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Background: Safety of anti-EGFR necitumumab (neci) was evaluated in combination with anti-PDI pembrolizumab (pembro) in pre-treated Stage IV NSCLC patients (pts).

Methods: Single-arm, multicenter Phase 1b study with expansion cohort to investigate the safety and effectiveness of neci combined with pembro in pts with Stage IV NSCLC. Part A: escalating doses of neci (600 mg and 800 mg IV) were administered on Day 1 and every 3 weeks (Q3W) in combination with pembro (200 mg IV) on Day 1 Q3W. Part B: expansion cohort with neci at dose identified in Part A administered with pembro. Major eligibility criteria included progression after 1 platinum-based chemotherapy and ECOG PS 0-1. Tumor tissue was collected for analysis of biomarkers. Treatment continued until disease progression or unacceptable toxicity.

Results: Part A completed without dose-limiting toxicity. As of 11 Feb 2016, 18 pts (neci 600 mg n = 3, 800 mg n = 15) were eligible for inclusion. Patients were female 44.4%, had median age 66.5 years [range 48-76], and adenocarcinoma histology 77.8%. All pts experienced ≥1 treatment-emergent adverse event (AE) with ≥1 related to study treatment. Four serious AEs occurred in 3 (16.7%) pts (all respiratory and mediastinal), none were treatment-related. No discontinuations or deaths were attributable to AEs. AEs occurring with ≥15% frequency are listed (table). Four (22.2%) pts experienced grade 2 AEs: acute respiratory failure, hypokalemia, hypophagia, ataxia, infusion-related reaction, pulmonary embolism, and hypophosphatemia.

Conclusions: The combination neki and pembro appears tolerable. The safety profile corresponds to individual profiles for both drugs, with no additive toxicities.

Clinical trial identification: NCT02451930

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company


Table: 1260P Treatment-emergent AEs of frequency >15%, n (%) MedDRA preferred term Interim safety population (N = 18)

Dermatitis acneform 16 (88.9)
Dry skin 8 (44.4)
Asthenia 7 (38.9)
Appetite decreased 4 (22.2)
Constipation 4 (22.2)
Headache 4 (22.2)
Hypophagia 4 (22.2)
Hypophosphatemia 4 (22.2)
Pruritus 4 (22.2)
Anemia 3 (16.7)
Diarrhoea 3 (16.7)
Dysponea 3 (16.7)
Fatigue 3 (16.7)
Hypokalemia 3 (16.7)
Respiratory tract infection 3 (16.7)
Stomatitis 3 (16.7)

Erlotinib in routine clinical practice for first-line maintenance therapy in patients with advanced non-small cell lung cancer (NSCLC)

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Background: The non-interventional study ML2816 is aimed at evaluating effectiveness and tolerability of 1 Erlotinib maintenance in clinical practice in patients with stable disease stage IIIb/IV NSCLC after 4 cycles of platinum-based chemotherapy.

Methods: The study included 272 unselected patients in 95 centers from 08/2010 to 05/2013. For each patient baseline characteristics, treatment regimen, effectiveness and safety data were collected. Data must be interpreted with caution as due to slow recruitment the study did not enroll 600 patients as planned. Primary endpoint was overall survival (OS). Sample size calculation was based on 1-year survival rate (SR).

Results: Mean patient age was 65 years. 19% of patients were non-smokers, 49% ex-smokers, 29% current smokers. 104 patients were evaluated for presence of EGFR mutations: 20 patients (19%) were EGFR mutation positive (EGFRmut+) and 84 (81%) EGFR-wildtype. 62% of patients had confirmed adenocarcinoma, 27% squamous cell and 4% large-cell carcinoma. Median OS from Erlotinib treatment start (ITT population) was 10.4m (95%-CI: 8.8 - 12.5m), and thus slightly below the results of the phase III SATURN trial (12.0m). The mPFS of 4.8m (95%-CI: 3.9-5.5m) was a little longer than in the SATURN trial (12.3 weeks; approx. 3.1m). The 1-year SR (ITT population) was 46% (95%-CI: 38 - 54%). EGFRmut+ status was significantly higher in patients with confirmed EGFR mutation status.
associated with longer OS and PFS (Cos.Regr. p = 0.031, PFS = 0.038 OS). For EGRFrmt vs. EGFR-Wildtype mPFS was 9.5m and 3.7m (log-rank p = 0.009), mOS was not reached and 7.8m (log-rank p = 0.061), respectively. 459 treatment-related adverse events (AE) were documented in 148 patients (54.4%), the most common rash (36.9%) and diarrhea (18.8%). 14 patients (3.1%) died due to a treatment-related AE. No new safety signals were detected.

Conclusions: Safety and effectiveness results of the study are in line with data of the SATURN trial. Improved PFS may be due to enrichment in EGRFrmt+ patients. EGRFrmt+ status was associated with improved PFS and OS. Of note, to reflect the findings of the IUNO trial (NCT01328951), the EU label of 1L Erlotinib maintenance was restricted in 01/2016 to patients with activating EGFR-mutations.

Clinical trial identification: ClinicalTrials.gov NCT0194050

Legal entity responsible for the study: Roche Pharma AG

Disclosure: P. Staib: Membership on an advisory board or board of directors: Roche, Celgene, Novartis, Amgen; Corporate-sponsored research: Celgene, Roche, Novartis, Amgen. W. Brugger: Membership on an advisory board or board of directors: Roche, BI, Lilly, AstraZeneca, Novartis, Pfizer; Other substantive relationships: Employee Astra Zeneca Cambridge since January 2016. All other authors have declared no conflicts of interest.

1263P

Updated efficacy and safety from the global phase II NP28673 study of alectinib in patients (pts) with previously treated ALK+ non-small-cell lung cancer (NSCLC)


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Background: Alectinib is an FDA-approved ALK inhibitor for pts with ALK+ NSCLC who have progressed on, or are intolerant to, crizotinib. Alectinib has shown systemic and CNS activity in previously treated pts in a pivotal phase II trials (NCT03810011 [NP28673] and NCT01810180 [NP28761]). We report updated safety and efficacy (data cut-off 01 Feb 2016) from the global NP28673 study (previously at ECC 2015 [Barlesi et al.]).

Methods: Pts ≥18 yrs, EGOG PS 0–2 confirmed ALK+ NSCLC (by FDA-approved FISH) previously treated with alectinib received alectinib 600mg BID in a 2:1 allocation. Median follow-up was 18.1+ months (range 1.1–54.1 months).

Results: 138 pts were enrolled (ITT), median age 52 yrs; 110 had received prior chemo, 84 (85.3%) included duration of response (DOR); PFS; OS; and safety (CTC v4.0).


<table>
<thead>
<tr>
<th>Backgr</th>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK+ NSCLC</td>
<td>Partial response, n (%)</td>
<td>7 (21)</td>
</tr>
<tr>
<td></td>
<td>Complete response, n (%)</td>
<td>3 (10)</td>
</tr>
<tr>
<td></td>
<td>Stable disease, n (%)</td>
<td>19 (62)</td>
</tr>
<tr>
<td></td>
<td>Median DOR, mos (95% CI)</td>
<td>11.7 (9.1–NE)</td>
</tr>
</tbody>
</table>

Conclusions: The updated NP28673 data show that alectinib is well tolerated and efficacy is robust, both systemically and in the CNS. The ongoing phase III ALEX trial is evaluating alectinib vs crizotinib in a first-line setting.

Clinical trial identification: NCT01810111 [NP28673] and NCT01871805 [NP28761]

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd


1264P

Automated nCounter-based assay for identifying clinically relevant ALK, ROS1 and RET rearrangements in advanced non-small-cell lung cancer (NSCLC)

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Background: Targetable rearrangements in anaplastic lymphoma kinase (ALK), ROS1, and RET genes can be detected in ~5–7% of patients with advanced NSCLC. Fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC) are currently used for screening but present disadvantages in terms of sensitivity, reproducibility, cost and throughput. The Elements nCounter multiplexed platform has the potential for quick, sensitive, and specific detection of clinically relevant fusion transcripts, but it needs validation in the clinical setting.

Methods: A set of probes for detection of ALK, ROS1 and RET fusion transcripts were designed and initially assessed in a panel of cell lines. Subsequently, a total of 108 FFPE samples from advanced NSCLC patients were analyzed with the nCounter multiplexed platform. Results were compared with FISH, IHC and, in the case of ALK, RT-PCR.

Response to crizotinib was retrospectively collected in a subset of patients.

Results: All patients categorized as positive for ALK by nCounter were concordant with IHC (100% sensitivity [CI = 88.3-100], 97.2% specificity [CI = 85.8-99.9]) while 10/31 were negative by FISH (95.5% sensitivity [CI = 78.2-99.2], 84.9% specificity [CI = 74.3-91.6]). Twenty patients received crizotinib based on ALK results and 18 derived clinical benefit. Of those, all were positive by nCounter while 3 were negative or not evaluable by FISH. In the case of ROS, 19/21 positive patients by nCounter were also positive by FISH (96.1% sensitivity [CI = 88.4-98.9]) but 8 samples were found positive by FISH and negative by nCounter (7.4% specificity [CI = 0.4-23.4]). Six of them were also negative by IHC, indicating lack of protein expression. Ten patients received crizotinib based on ROS results. Of the seven patients deriving clinical benefit, six were positive by nCounter. Two patients were nCounter positive for RET, one of them was FISH positive.

Conclusions: We have validated an ALK/R0S1/RET nCounter multiplexed assay that allows for effective screening of FFPE samples and identifies advanced NSCLC patients who will benefit from targeted therapies.

Legal entity responsible for the study: N/A

Funding: Fundación Clinic, Hospital Clinic, Barcelona, Spain

Disclosure: All authors have declared no conflicts of interest.

1265P

Non-invasive detection of response and crizotinib induced resistance in ROS1 fusion advanced stage Chinese lung adenocarcinoma patients using next-generation genotyping from cfDNA

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Background: Recently Crizotinib has exhibited marked therapeutic efficacy in the treatment of the advanced stage ROS1 fusion non-small-cell lung cancer (NSCLC). However, the challenge of acquired resistance to Crizotinib in ROS1 fusion NSCLC has been an issue, and the invasive nature of obtaining a second tissue biopsy does not allow for straightforward monitoring of disease status. Cell free plasma DNA (cfDNA) is a promising biomarker for non-invasive assessment of cancer burden. This study
Clinical analysis of continuing crizotinib treatment beyond disease progression in ALK-positive non-small-cell lung cancer patients

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Background: Continuing the treatment of tyrosine kinase inhibitors (TKIs) after disease progression (PD) in EGFR mutation-positive non-small-cell lung cancer (NSCLC) is recommended in the guidelines. However, the evidence for the efficacy and safety of TKI continuation after PD is limited.

Methods: We retrospectively analyzed the continuation of crizotinib treatment beyond PD in 44 ALK-positive NSCLC patients who were treated with crizotinib. The patients who continued crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010). Multivariate Cox regression analysis indicated that the continuing crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010). Multivariate Cox regression analysis indicated that the continuing crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010). Multivariate Cox regression analysis indicated that the continuing crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010). Multivariate Cox regression analysis indicated that the continuing crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010). Multivariate Cox regression analysis indicated that the continuing crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010).

Results: Of 108 patients screened, 53 patients got PD at the cutoff time. Median follow-up was 12.3 months. After PD, 23 patients continued discontinued crizotinib treatment and 30 patients continued baseline treatment. Baseline characteristics showed that continued ones had a better ICGO performance status than discontinued ones (P = 0.006). Patterns of PD was significantly different in two groups (P = 0.001). Median PFS and median OS were 6.6 months (95% CI 5.2-8.4) and 14.6 months (95% CI 10.1-19.1), respectively. In 23 discontinued ones, median PFS was 6.8 months (95% CI 5.4-8.2) and 30 in continued ones, median PFS and median OS were 6.2 months (95% CI 2.6-9.7) and 6.1 months (95% CI 4.5-7.7), respectively. The patients who continued crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010). Multivariate Cox regression analysis indicated that the continuing crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010). Multivariate Cox regression analysis indicated that the continuing crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010). Multivariate Cox regression analysis indicated that the continuing crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010). Multivariate Cox regression analysis indicated that the continuing crizotinib treatment had a significantly longer median OS than those discontinued (18.4 versus 9.9 months, P = 0.010).

Conclusions: ALK-positive NSCLC may get clinical benefits from the continuation of crizotinib beyond PD, especially in those patients with brain or bone metastases.

Legal entity responsible for the study: Dr. Lingmei Hong

Disclosure: All authors have declared no conflicts of interest.
these patients (pts) outside patients included in clinical trial. Objective: to investigate clinical characteristics and management of these patients in real world setting.

Methods: Inclusion of pts with a diagnosis of NSCLC harboring BRAF mutations between January 2012 and December 2014, collection of demographic and clinical characteristics, risk factors, Progression Free Survival (PFS), Overall Survival (OS), mode of progression and therapeutic management, sub group analysis according to the BRAF mutation (V600E versus others).

Results: 59 patients recruited in 24 centers: 34 (57.6%) men; age 64.5 ± 14.5 years; P01 at diagnosis: 42% current/former smokers; 23 (40.3%)/18 (32.6%); adenocarcinoma: 93%; Stage at diagnosis 4/3/2: 77%/16%/7%; Braf V600E: 81%; co-mutations EGFR n = 2, ALK n = 2. Outcomes of stage IV (n = 44): first line treatment: chemotherapy: 61.9%, chemotherapy + radiotherapy: 9.5%, radiotherapy alone: 2.4%. Best supportive care (BSC): 11.9%, anti BRAF: 4.2% response rate and PFS to first line treatment: 51.7% and 8.7 months (CI 6.4; 13.2), second line treatment (n = 21): chemotherapy: 66.7%, anti BRAF 23.8%, BSC 8.9%, response rate and PFS to second line treatment: 33.3% and 4.8 months (CI 2.7;10.3), 2 years OS: 58.5% (CI 45.8; 74.3); 17 pts received BRAF inhibitor. Outcome of stage IV Braf harboring V600 E (n = 32) didn't show any significant difference

Conclusions: In this real world analysis, the majority of NSCLC patients with BRAF mutation, smokers and men appears and appears to have a better survival to NSCLC pts without oncogenic driver.

Clinical trial identification: EXPLORE GPCC 02-14 comité d’Ethique du CHU de Saint-Eloi Commission recherche de Terre d’éthique: IRB N 2010/0016/CHU/STE

Legal entity responsible for the study: N/A

Funding: Clinical trial information: Supported by an academic grant from Lilly, Astra Zeneca, boehringer ingelheim

Disclosure: J.B. Auliac: In the last five years, honoraria for attending scientific meetings, speaking, organizing research or consulting, from Boehringer Ingelheim, Hoffman–Roche, Lilly and Pfizer. A. Vergnenegre: In the last five years, Honoraria for attending scientific meetings, speaking, organizing research or consulting, from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffman–la Roche, Sanofi Aventis, Lilly, Novartis and Agen. All other authors have declared no conflicts of interest.

 ALTER 2689

SELECT-3: A Phase I study of selumetinib in combination with platinum doublet chemotherapy for advanced NSCLC in the first-line setting


Methods: In a Phase I study of patients (pts) with KRAS-mutant advanced NSCLC in the second-line setting. This study investigated selumetinib plus platinum doublet chemotherapy as first-line treatment for pts with advanced/metastatic NSCLC, unscheduled for KRAS mutation status.

Results: In total, 55 pts were treated (26 female, median age 62 years, 38 adenocarcinoma, 13 squamous) in seven cohorts: C1 (C3 sel507 + gem + cis, n = 37); C2 sel507 + gem + carb, n = 8; C4/C5 sel507/570 + gem + carb, n = 34/36; C6 sel570 + gem + cis, n = 15. Median total selumetinib exposure was 84 days (range 4–266). Most frequent AEs were fatigue, nausea, diarrhoea and vomiting. Grade (G) ≥3 selumetinib-related AEs were seen in 10 (53%) pts. Dose-limiting toxicities (DLTs, all n = 1) were reported in: C2, G4 thrombocytopenia/epistaxis and G4 thrombocytopenia, C3, G4 anaemia, C3, G3 leucy, C7, C4 febrile neutropenia. Nine pts died during the study; none were causally related to selumetinib. Selumetinib PK was similar across the combination regimens. Of the 55 patients treated, confirmed partial responses were observed in 11 (20%) pts and 9 (16%) pts, and 21 (38%) pts had stable disease (26 weeks).

Conclusions: In the first-line setting, RPDs were identified as selumetinib 75 mg BID plus standard doses of gem + carb or pem + cis, which were tolerated with AE profiles consistent with the individual agents. RPDs were not identified for gem containing regimens. Preliminary anti-tumour activity was observed across all cohorts. We thank
KRAS mutations (m) in lung adenocarcinoma (AC) patients (p) receiving standard chemotherapy (ch) and immune checkpoint inhibitors (i-CI): Impact of KRAS clonality and coexisting TP53m

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Background: RASm the most frequent oncogene alteration in ADC is not directly targetable with agents currently available for clinical use. We studied the efficacy of ch and i-CI in RASm ADC and explored a potential effect of clonality of KRASm and coexisting KRASm/TP53m in outcome

Methods: Out of 250 AC p with targeted mut profiling (Sequenom/Amplicon Seq/3) 63 (25%) were eligible for retrospective analysis of clinical endpoints. Primary endpoints: to determine progression-free survival (PFS) on first-line platinum-based ch plus maintenance 2PFS on subsequent i-Ci as single agent, OS in metastatic setting (metOS) Secondary endpoints: to correlate survival endpoints with the clonality of KRAS mut allele fractions (MAFs, adjusted for tumor purity in the sample) and coexisting TP53m

Results: Median age was 58yrs (range 33-75) 35male (55%) 24 (38%) at diagnosis and in remaining pts, median time from diagnosis to relapse was 10 months (7-16) 63p by 73% of EGFR and 58% of KRASm tumors, most frequent variants being G12C(20) G12V(10) G12D(9) G12other (6) G13(6) Q61(5) while 2p had NRASm tumors (Q61) with G12D(9) G12other(6) G13(6) Q61(5) Median MAF was 0.44(0.32-0.55) with no differences in primary tumor (0.42 ± 0.36) or metastatic site biopsy (0.41 ± 0.5). 19% of samples had MAFs < 0.25 considered subclonal. 40p received first-line platinum-based ch median PFS was 6.7m (1.8-2.2) and did not significantly change if subclonal KRASm allele (p = 0.72) or coexisting TP53m (p = 0.51). Median PFS in 17p that received i-CI (17pvalumab 17azolomab 2pembroluzimab 1avelumab) was 3.2m (3.1- not reached) with 22% of p at 17p. Coexisting KRASm/TP53m clonality (p = 0.39) and coexistence of TP53m (p = 0.15) did not affect PFS on i-CI. Median metOS was 30.5m (15.2- not reached) without significant differences if subclonal KRAS m triplets (p = 0.88) or coexisting TP53m (p = 0.55)

Conclusions: KRAS mutated AC p have favorable outcomes when exposed to standard ch and i-CI. The majority of samples present KRAS MAFs suggesting clonal (truncal) events. TP53m is the most common coexisting driver alteration. In our exploratory cohort, these factors did not impact treatment benefit of ch, i-CI or survival in the metastatic setting

Legal entity responsible for the study: N/A

Funding: VHI

Disclosure: All authors have declared no conflicts of interest.

Cost of care in first line advanced NSCLC patients: Chemotherapy vs targeted therapy

J. Radtchenko1, B. Korytovsky2, K. Turel, B. Mwir2, B. Feinberg1
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Background: Targeted therapies have increasingly placed drug cost in the spotlight. This represents only one aspect of cancer treatment cost. To provide a comprehensive view, we analyzed first-year drug costs, procedures and acute care interventions for a NSCLC patients on chemo vs TT in the 1L setting.

Methods: Using Inovalon’s MOB® Registry US claims data, aNSCLC pts were identified by International Classification of Diseases-9 codes from July 2013 to June 2014. Inclusion: all NSCLC pts >18 years who received 1L systemic therapy within 6 months (mo) of diagnosis. Exclusion: pts with small-cell lung cancer or secondary malignancies, clinic trial pts, pts with <12 mo follow-up, and cost outliers (2.5% on both ends of the cost curve). Wholesale acquisition cost (WAC) and average sales price (ASP) were used to determine drug costs; the Medicare Physician Fee Schedule (MPFS) and Hospital Outpatient Prospective Payment System (OPPS) were used for procedure costs. Descriptive statistics were used to analyze costs from 1L start to beginning of second line (2L) treatment or last claim if 2L therapy was not initiated within the 12 mo follow-up. TT included erlotinib, cetuximab, afatinib, crizotinib or bevacizumab-monomotherapy.

Results: Of 5319 1L pts, 1070 (20%) had ≥12 mo of follow-up and were included in the analysis. Of those, 23% received TT (242 pts); 625 (60%) incurred treatment costs. Results of the analysis are presented in the table.

Table: 1273P

<table>
<thead>
<tr>
<th></th>
<th>All pts</th>
<th>TT pts</th>
<th>Chemo pts</th>
</tr>
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<tbody>
<tr>
<td>Mean follow-up, mo</td>
<td>20.3</td>
<td>21.7</td>
<td>20.1</td>
</tr>
<tr>
<td>Mean 1L TC, $</td>
<td>110,138</td>
<td>118,898</td>
<td>108,624</td>
</tr>
<tr>
<td>Mean 1L TC monthly, $</td>
<td>5,414</td>
<td>5,595</td>
<td>4,996</td>
</tr>
</tbody>
</table>

Conclusions: The study showed considerable TC in 1L NSCLC, with systemic therapy representing a significant share. Pts with inpatient care incurred higher TC, and chemo pts had a higher share of inpatient costs vs TT pts. Alternatives to traditional chemo may allow for savings across non-drug-related outpatient and inpatient costs.

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: J. Radtchenko. Participation in funded or unfunded research on a technology, process, or product development or are the principal investigator for a project related to research from Cardinal Health, analyst and study director. B. Korytovsky, K. Turel. Employment and Stock or Other Ownership from BMS. All other authors have declared no conflicts of interest.

Analysis of outcomes and brain metastases (BM) of molecular selected non-small cell lung cancer (NSCLC) patients included in clinical trials

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Background: The molecular profiling of patients (p) with advanced NSCLC identifies several oncogenic drivers that can be targeted with selective inhibitors. We aimed to assess the characteristics and prognostic factors of p with molecular alterations at our center treated with targeted agents.

Methods: EGFR, KRAS, HER2 mutated p and ALK, ROS1 and RET rearrangements positive p enrolled onto clinical trials between 2009 and 2015 at our center were included in this analysis. A cohort of wild type (WT) adenocarcinoma p was selected as comparator. Survival was estimated by the Kaplan-Meier method.

Results: 200 p were collected (76 WT, 45 EGFR, 53 ALK, 21 KRAS, 3 ROSI, 2 HER2 and 2 RET). Median age 57 years (26-82), 52% men, 60% performance status (PS) 1, 59% smokers, 98% stage IV and 92% adenocarcinoma. First treatment was selective inhibitor in 73% of EGFR and 58% of ALK p. Median follow up was 23 mo (95% CI 1.6-104.6). The overall survival (OS), still immature with 58% of deaths, was 33mo for all p and 57m EGFR, 40m ALK, 31m KRAS and 19m WT. We found differences in OS for molecular selected population vs WT (55m vs 19 m p = 0.001), women (55m vs 23m, p = 0.002), PS 01 vs PS2 (21 vs 7m, p < 0.001) and non-smokers (51 vs 23m smokers, p = 0.002). Brain metastases were detected in 86 p (36 ALK, 25 WT, 14 EGFR, 8 KRAS, 2 ROS1 and 1 RET) and 87% received local therapy. BM were more frequent in women, non-smokers and ALK p (p < 0.001). BM developed at a median of 6m from diagnosis of NSCLC (6m molecular selected and 5m WT, p = 0.44) and median OS after development of BM was 14m (28m EGFR, 26m ALK and 8m WT, p < 0.001). No differences in OS were detected in p with or without BM (p = 0.05).

Independently of target agent, we did not found significant differences in OS with BM treated with local therapy vs systemic treatment (p > 0.005). P who initiated the EGFR and ALK inhibitors after diagnosis of BM had greater benefit than those p who began treatment before diagnosis of BM (86m vs 57m for EGFR and 35m vs 5m for ALK respectively, p > 0.05 in both).

Conclusions: Molecular selected p treated with targeted agents have prolonged survival. Brain metastases is a frequent site of disease progression, but the prognosis of these p is impressive independently of local therapies.

Legal entity responsible for the study: N/A

Funding: VHI

Disclosure: All authors have declared no conflicts of interest.
Background: The PI3K/akt pathway is a promising target in NSCLC, especially in squamous (sq) tumors which show high frequencies of PI3K mutations and PTEN deletions. Epithelial growth factor receptor (EGFR) is also expressed in sq NSCLC tumors, and when treated with EGFR inhibitors, PI3K/Akt is up-regulated. In a sq NSCLC xenograft model, combination therapy with the EGFR monoclonal antibody, Necitumumab (Neci), and the PI3K/mTOR dual inhibitor, LY3023414 (LY), causes synergistic tumor regression. We initiated a phase 2 study evaluating these agents in pts with sq NSCLC. Here we report the first-in-human lead-in portion of the study.

Methods: Patients (pts) with metastatic sq NSCLC after platinum-containing therapy for advanced disease were eligible. Prior immunotherapy was allowed. Pts who developed venous thromboembolism within 3 months prior to screening or had uncontrolled diabetes were excluded. Pts received LY 200 mg PO BID on days 1-21 and Neci 800 mg IV d1 and d8 of a 21 d cycle until disease progression or intolerable toxicity. Tumor assessments were performed every 6 weeks. Pts who had received ≥75% of the 1st cycle of treatment (tx) were considered evaluable for safety.

Results: Fifteen pts were treated in the safety lead-in. Median age was 66, 86 % (13 pts) were male, 73 % (11 pts) were current or former smokers, and all had ECOG performance status 0-1. Seven pts were evaluable for safety. There were no dose-limiting toxicities and no serious tx-related adverse events (TRAEs). Common TRAEs are summarized in Table 1. Single-agent toxicity was not synergistic. Median duration of tx was 5 weeks (range 1-19+ weeks). Six pts remain on tx.

Conclusions: The combination of Neci and LY in sq NSCLC has preclinical rationale, appears to be safe and tolerable in patients, and is without overlapping toxicities. Enrolment of the post lead-in cohort to determine efficacy in a total of 48 pts is on-going.

Clinical trial identification: NCT02443337

Legal entity responsible for the study: Clinical Trials.gov

Funding: Eli Lilly and Company


**Table: 1274P**

<table>
<thead>
<tr>
<th>TRAE in ≥10% of pts, n (%)</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acneiform Rash</td>
<td>7 (47%)</td>
<td>1 (7%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (27%)</td>
<td>1 (7%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (27%)</td>
<td>1 (7%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3 (20%)</td>
<td>3 (20%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (20%)</td>
<td>3 (20%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>1 (7%)</td>
<td>1 (7%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (13%)</td>
<td>0</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Chills</td>
<td>2 (13%)</td>
<td>0</td>
<td>2 (13%)</td>
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<tr>
<td>Hypomagnesemia</td>
<td>2 (13%)</td>
<td>0</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1 (7%)</td>
<td>1 (7%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (13%)</td>
<td>0</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Weakness</td>
<td>2 (13%)</td>
<td>0</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>2 (13%)</td>
<td>0</td>
<td>2 (13%)</td>
</tr>
</tbody>
</table>

**Methods:** Randomized trials of AD plus standard second-line treatment, CT (docetaxel [Do], pembrolizumab) or E plus compared to same standard treatment ending accrual before 2015 were included based on search of publication databases, abstract proceedings and trial registers. Data were extracted from publications. Random-effect models, in case of significant heterogeneity (Het), fixed-effect model otherwise, were used to compute pooled hazard ratios (HRs) for overall survival (OS, primary end-point) and PFS and pooled odds ratios (ORs) for response rate (RR) and adverse events. Her was studied using Q-test 1.

**Results:** Seventeen trials with 8,703 patients were included with 3 types of combinations: 5 trials monoclonal antibodies AD + CT (Do for 5), 7 on tyrosine kinase inhibitor (TKI) AD + CT (Do for 3) and 5 AD (TKI for 4) + E. Trial size ranged from 100 to 191 patients. ADs evaluated were: cabozantinib (1 trial), afibrecet (1), nintedanib (2), ramucirumab (2), sorafenib (1), bevacizumab (3), vandetanib (3), sintuitin (3), control arm was docetaxel (8 trials), pembrolizumab (4), E (5). Compared with standard second-line treatment alone, AD significantly prolonged OS (HR 0.94 [95% confidence interval 0.89-0.99], random-effect model; P = 0.03; P-Het = 0.042), PFS (0.79; [0.73–0.85], random effect model; P < 0.0001; P-Het = 0.003), and improved RR (OR: 1.86 [1.62-2.12], fixed-effect model; P < 0.0001; P-Het = 0.39) with no difference in the benefit in OS, PFS and RR between the 3 types of combination tested.

**Conclusions:** Antiangiogenic drugs significantly prolong OS and PFS when added to standard second-line treatment in advanced NSCLC patients. Toxicity results will be presented during the congress.

Legal entity responsible for the study: N/A

Funding: Gustave Roussy

Disclosure: All authors have declared no conflicts of interest.

**Efficacy and safety of nintedanib (NIN)/docetaxel (DOC) in patients with lung adenocarcinoma: Further analyses from the LUME-Lung 1 study**

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Background: NIN is a triple angiokinase inhibitor approved in the EU in combination with DOC for the treatment of adenocarcinoma non-small cell lung cancer patients after first-line therapy (FLT). A continuous linear correlation between overall survival (OS) benefit with NIN and the predictive marker “time from start of FLT” (TSFLT) has been observed in adenocarcinoma patients. Methods: First, analyses were conducted of European adenocarcinoma patients, who comprise the majority of the population from the Phase III LUME-Lung 1 trial comparing NIN/DOC with placebo (PLA)/DOC (NCT00805194). Second, in order to further characterise time from FLT, analyses were conducted in adenocarcinoma populations defined by the dichotomisation at appropriate cut-points of TSFLT or progressive disease (PD) as best response to FLT. Analyses based on “time from end of FLT” (TEFLT) as described in other clinical trials were also performed.

**Results:** In the overall adenocarcinoma population (n = 658), both independently assessed progression-free survival (median 4.9 vs 2.8 months, hazard ratio [HR] 0.77 [95% CI 0.66–0.90, p = 0.0195] and OS were significantly longer with NIN/DOC vs PLA/DOC (median OS of [mos] 12.6 vs 10.3 months, HR 0.83 [95% CI 0.70–0.99]; p = 0.0359). OS improved both in the overall European adenocarcinoma (n = 463; mos 13.4 vs 8.7 months, HR 0.79 [0.65–0.97]; p = 0.0244) and in European adenocarcinoma patients with TSFLT < 9 months (n = 271; mos 11.0 vs 6.9 months, HR 0.69 [0.53–0.98]; p = 0.0489). In the overall adenocarcinoma population, OS also improved in patients with TSFLT < 9 months (n = 405; mos 10.9 vs 7.9 months, HR 0.75 [0.60–0.92]; p = 0.0073), TESFLT < 6 months (n = 232; mos 9.5 vs 7.5 months, HR 0.73 [0.55–0.98]; p = 0.0327), and PD to FLT (n = 117; mos 9.8 vs 6.3 months, HR 0.62 [0.41–0.94]; p = 0.0246). Analyses based on TESFLT provided additional insights to TSFLT. Adverse events (AEs) reported with NIN included manageable gastrointestinal AEs and liver enzyme elevations.
Conclusions: Ninety-three percent of patients achieved response, and most patients tolerated treatment well. Addition of pembrolizumab to historical controls of pembrolizumab as a single agent shows a promising increase in overall survival.

Clinical trial identification: NCT02289456

Legal entity responsible for the study: N/A

Funding: Celgene Corporation

Disclosure: A. Gajra, Consultant to Celgene Corporation. K.I. Amiri, T.J. Ong, A. Sanford: Employee of Celgene and owns stock. N. Abdel Karim: Advisory for Pfizer, Prometheus, Novartis and Bayer. E. Santos: Member of the following Speakers’ Bureau: Celgene. F. Michieli, A. Lichter, Genetech. L. B., W. M. Millennium, M. Schöffel New York, Syracuse, NY, USA, 2Hematology, Henry Ford Hospital, Detroit, MI, USA, 3Medical Affairs, Celgene Corporation, Summit, NJ, USA, 4Oncology, University of Cincinnati, Cincinnati, OH, USA, 5Oncology, Ochsner Medical Center, New Orleans, LA, USA, 6Hematology/Oncology, University of Rochester Medical Center, Rochester, NY, USA, 7Medicine, Eugene M and Christine E Lynn Cancer Center, Boca Raton, FL, USA, 8Medical Oncology, University of Pittsburgh UPMC Cancer Pavilion, Pittsburgh, PA, USA, 9Oncology, Sarah Cannon Research Institute, Nashville, TN, USA, 10Oncology, Yale Cancer Center, New Haven, CT, USA

Background: Pts with poor PS can benefit from combination chemotherapy; however, they may be at greater risk for toxicity vs pts with good PS. Here, we report interim safety results in pts with advanced NSCLC and an EOCG PS 2 treated with nab-P/C followed by nab-P monotherapy.

Methods: Pts with stage IIIIB/IV NSCLC, no prior anti-cancer therapy for metastatic disease, and an EOCG PS 2 received nab-P 100 mg/m² d 1 and 8 + C area under the curve 5 d (21-d cycles) for 4 cycles. Starting at cycle 5, pts without progression could continue nab-P 100 mg/m² monotherapy d 1 and 8 (21-d cycles) until progression/ unacceptable toxicity. The primary endpoint is percentage of pts discontinuing treatment during the first 4 cycles due to treatment-emergent adverse events (TEAEs).

Results: As of April 4, 2016, 31 pts were treated. Median age was 71 y, 61% were male, 61% had nonsquamous NSCLC, and 39% had squamous NSCLC. Overall, 14/31 pts remained on therapy at the time of this analysis; 13 pts discontinued in the first 4 cycles and 4 pts from cycle 5 onwards (5 due to AEs, 5 due to progression, 4 due to pt decision, 2 due to symptomatic deterioration, and 1 due to other reasons). In all treated pts, the median percentage of per-protocol dose of nab-P was 85%. Dose adjustments included at least 1 nab-P dose not administered, dose delay, or dose reduction (13, 12, and 7 pts, respectively). Overall, the median dose intensity for nab-P was 56.58 mg/m² week (expected: 66.7 mg/m²/week). Serious TEAEs occurred in 48% of pts; the incidence of each individual serious TEAE reported was < 10%. In all pts, grade ≥ 3 TEAEs of special interest included neutropenia (26%), dyspnea (13%), and anemia (10%); grade ≥ 3 peripheral neuropathy was noted in 1 pt. Radiological response was observed in 5/22 pts (pending confirmation) and 13/22 pts achieved stable disease.

Conclusions: Pts with PS 2 are at risk for greater toxicity with combination therapy, but these interim results indicate that a tailored nab-P/C regimen is feasible with a manageable safety profile, and may be an appropriate treatment option regardless of histology. NCT02289456

Clinical trial identification: NCT02289456

Legal entity responsible for the study: N/A

Funding: Roche Pharma AG

Disclosure: H. R. Wirtz: Membership on an advisory board or board of directors: MSD, Roche. Boehringer Ingelheim Corporate-sponsored research. TNI Medical. S. Lang, S. Hammerschmidt: Membership on an advisory board or board of directors: Roche. M. Reck: Membership on an advisory board or board of directors: Hoffmann-La Roche, Lilly, MSD, Astra Zeneca, BMS, Pfizer, Novartis, Celgene. Boehringer Ingelheim. All other authors have declared no conflicts of interest.

1277P Interim safety results from the phase 2 ABOUND.PS2 study evaluating nab-paclitaxel (nab-P) + carboplatin (C) followed by nab-P monotherapy in patients (pts) with NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2


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Background: Pts with poor PS can benefit from combination chemotherapy; however, they may be at greater risk for toxicity vs pts with good PS. Here, we report interim safety results in pts with advanced NSCLC and an EOCG PS 2 treated with nab-P/C followed by nab-P monotherapy.

Methods: Pts with stage IIIIB/IV NSCLC, no prior anti-cancer therapy for metastatic disease, and an EOCG PS 2 received nab-P 100 mg/m² d 1 and 8 + C area under the curve 5 d (21-d cycles) for 4 cycles. Starting at cycle 5, pts without progression could continue nab-P 100 mg/m² monotherapy d 1 and 8 (21-d cycles) until progression/ unacceptable toxicity. The primary endpoint is percentage of pts discontinuing treatment during the first 4 cycles due to treatment-emergent adverse events (TEAEs).

Results: As of April 4, 2016, 31 pts were treated. Median age was 71 y, 61% were male, 61% had nonsquamous NSCLC, and 39% had squamous NSCLC. Overall, 14/31 pts remained on therapy at the time of this analysis; 13 pts discontinued in the first 4 cycles and 4 pts from cycle 5 onwards (5 due to AEs, 5 due to progression, 4 due to pt decision, 2 due to symptomatic deterioration, and 1 due to other reasons). In all treated pts, the median percentage of per-protocol dose of nab-P was 85%. Dose adjustments included at least 1 nab-P dose not administered, dose delay, or dose reduction (13, 12, and 7 pts, respectively). Overall, the median dose intensity for nab-P was 56.58 mg/m² week (expected: 66.7 mg/m²/week). Serious TEAEs occurred in 48% of pts; the incidence of each individual serious TEAE reported was < 10%. In all pts, grade ≥ 3 TEAEs of special interest included neutropenia (26%), dyspnea (13%), and anemia (10%); grade ≥ 3 peripheral neuropathy was noted in 1 pt. Radiological response was observed in 5/22 pts (pending confirmation) and 13/22 pts achieved stable disease.

Conclusions: Pts with PS 2 are at risk for greater toxicity with combination therapy, but these interim results indicate that a tailored nab-P/C regimen is feasible with a manageable safety profile, and may be an appropriate treatment option regardless of histology. NCT02289456

Clinical trial identification: NCT02289456

Legal entity responsible for the study: Roche Pharma AG

Funding: Roche Pharma AG

Disclosure: H. R. Wirtz: Membership on an advisory board or board of directors: MSD, Roche. Boehringer Ingelheim Corporate-sponsored research. TNI Medical. S. Lang, S. Hammerschmidt: Membership on an advisory board or board of directors: Roche. M. Reck: Membership on an advisory board or board of directors: Hoffmann-La Roche, Lilly, MSD, Astra Zeneca, BMS, Pfizer, Novartis, Celgene. Boehringer Ingelheim. All other authors have declared no conflicts of interest.
nab-paclitaxel (nab-P) + carboplatin (C) induction therapy in patients (Pts) with squamous (SCC) NSCLC: Interim safety outcomes from the phase 3 ABOUND.sqm study

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Background: Limited QoL data exist for pts with advanced NSCLC treated with platinum-doublets, though these assessments can help interpret the clinical benefit of chemotherapy. Interim QoL outcomes in pts with SCC NSCLC treated with nab-P/C during the induction part of the ongoing ABOUND.sqm study are reported here.

Methods: Pts with advanced SCC NSCLC received first-line nab-P 100 mg/m² d 1, 8, 15 + C area under the curve 4 d (21 cycles) for 4 cycles (induction). After 4 cycles, pts without progression continued to maintenance (randomized 2:1) nab-P 100 mg/m² d 1 and 8 of each 21-d cycle + best supportive care (BSC) or BSC alone until progression or unacceptable toxicity. Progression-free survival from randomization into the maintenance part of the study is the primary endpoint. QoL (an exploratory endpoint of induction and maintenance parts) was assessed on d 1 of each cycle using the Lung Cancer Symptom Scale (LCSS) and Euro-QoL-5 Dimensions-5 Levels (EQ-5D-5L). The pre-planned analysis reports interim QoL data from induction to data cutoff.

Results: 195 pts were included in this interim report, 90% completed baseline (BL) and 2 post-BL QoL assessments. The median age was 68 years, 65% were male, and 99% had 0-1 Eastern Cooperative Oncology Group performance status. During induction, the mean change from BL in LQSS symptom burden index and total score improved by ≥ 10.4% and ≥ 9.2%, respectively. Clinically meaningful improvements (≥ 10 mm [visual analog scale]) from BL in the individual LCSS items of cough, shortness of breath, and hemoptysis were observed in 50% of pts. More than 80% of pts maintained or improved each dimension of the EQ-5D-5L from BL. In pts with radiological stable disease or better (75/108 of 210 pts), 75% of pts observed in 50% of pts. More than 80% of pts maintained or improved each dimension of the EQ-5D-5L from BL. In pts with radiological stable disease or better (75/108 of 210 pts), 75% of pts experienced grade 3/4 peripheral sensory neuropathy.

Conclusions: These interim results of the ABOUND.sqm study indicate no new safety signals in pts with SCC NSCLC receiving nab-P/C induction therapy. Updated results will be presented at the meeting.

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Legal entity responsible for the study: N/A

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Disclosure: O.J. Vidal: D. Gianelli, M. Johnson, E. Anderson, S. Dakhil, R. Jotte, J. Knoble. Consultant to Cardinal Health; is a member of the following Speakers’ Bureau: Novartis, Celgene. A. Tscherne, T.J. Ong, M. Socinski: Honorarium from Celgene. J. Knoble: Consultant to Cardinal Health, is a member of the following Speakers’ Bureau: Novartis, Celgene. A. Tscherne, T.J. Ong, M. Socinski: Employee of Celgene, owns stock. All other authors have declared no conflicts of interest.

Quality of life (QoL) in elderly patients (Pts) with advanced NSCLC treated with nab-paclitaxel (nab-P) + carboplatin (C): Interim results from the ABOUND.70+ study


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Background: The lack of QoL assessment in elderly pts receiving chemotherapy for NSCLC is an important issue that potentially hinders treatment decisions. We report interim QoL outcomes in elderly pts with advanced NSCLC treated with nab-P/C in the ABOUND.70+ study.

Methods: Pts ≥ 70 years of age with locally advanced/metastatic NSCLC were randomized 1:1 to first-line nab-P 100 mg/m² d 1, 8, 15 + C area under the curve 4 d (21 cycles) + best supportive care (BSC). nab-P/C regimen followed by a 1 week break between cycles (arm B, every 28 days). The percentage of pts with either grade ≥ 2 peripheral neuropathy or grade 3 myelosuppression adverse events is the primary endpoint. QoL (an exploratory endpoint) was assessed using the Lung Cancer Symptom Scale (LCSS) and Euro-QoL-5 Dimensions-5 Levels (EQ-5D-5L) on d 1 of each cycle.

Results: Of 119 pts included in this report, > 85% completed baseline (BL) and > 70% completed BL + ≥ 1 post-BL QoL assessments. The median age was 76 years (range, 70-93 years), 56% were male, and 99% had an Eastern Cooperative Oncology Group performance status of 0-1. In general, LSQSS symptom burden index and total score improved during the first 4 cycles in the LCSS item of cough, a mean change from BL to end of cycle 4 of 18.89 points was observed on the visual analog scale (VAS), 95% CI, 5.42 - 32.45). Clinically meaningful improvements (≥ 10 mm [VAS]) from BL in the composite LCSS items of cough, shortness of breath, and hemoptysis were observed in 50% of pts. More than 80% of pts maintained or improved each dimension of the EQ-5D-5L from BL. In pts with radiological stable disease or better (75/108 of 210 pts), 75% of pts experienced grade 3/4 peripheral sensory neuropathy.

Conclusions: These interim results from the ABOUND.70+ study suggest that nab-P/C treatment resulted in clinically meaningful QoL improvements in elderly pts with NSCLC. The study is ongoing, and efficacy and safety data will be reported at future meetings.
A cross-trial comparison of pemetrexed-platinum followed by pemetrexed continuation maintenance versus gemcitabine-cisplatin without maintenance in chemotherapy-naive patients with advanced nonsquamous non-small-cell lung cancer

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Background: This cross-trial pooled analysis aimed to demonstrate improved efficacy of pemetrexed (pem) – platinum (plat) followed by pem continuation maintenance over gemcitabine (gem) – cisplatin (cis) without maintenance in advanced nonsquamous non-small-cell lung cancer (NSQ NSCLC) patients.

Methods: Analysis populations consisted of patients with similar baseline characteristics selected from 3 trials (JMDB, PARAMOUNT, and MIND) using a propensity score method. JMDB investigated first-line pem-cis (pem 500 mg/m² + cis 75 mg/m² every 21 days [q21d] for 6 cycles) and gem-cis (gem 1250 mg/m² on days 1, 8 and cis 75 mg/m² q21d for 6 cycles). PARAMOUNT compared pem maintenance vs placebo after patients with NSQ NSCLC completed 4 cycles of first-line pem-cis without progressive disease (PD). MIND examined pem-carboplatin (carb) (pem 500 mg/m² + carb area under the curve 6 mg/mL*min q21d for 4 cycles) induction therapy followed by pem maintenance in NSQ NSCLC patients. Kaplan-Meier method and Cox regression were used to analyze overall survival (OS) and progression-free survival (PFS).

Conclusions: This cross-trial analysis supports pem-plat induction followed by pem continuation maintenance therapy as a preferred choice over gem-cis without maintenance as first-line chemotherapy for patients with advanced NSQ NSCLC.


Legal entity responsible for the study: Eli Lilly and company

Funding: Eli Lilly and company

Disclosure: Y.-L. Wu: Ongoing unpaid consultant with Eli Lilly and MSD, and has received speaker fee from Eli Lilly, Roche, Boehringer Ingelheim, and AstraZeneca. B. Zhang, X. Wang: Currently employee of Eli Lilly and Company. M. Orlando, H. Chi: Employee and shareholders of Eli Lilly and Company.

The role of thymidylate synthase in non-small-cell lung cancer treated with pemetrexed continuation maintenance therapy

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Background: Pemetrexed continuation maintenance therapy has been proved to be beneficial for patients with advanced non-squamous NSCLC. The ongoing need to identify those patients who will benefit more from pemetrexed continuation maintenance suggests a more detailed research on resistance to pemetrexed is required. Our previous research has explored high expression of thymidylate synthase (TS) in pulmonary adenocarcinoma and shown it is associated with acquired resistance to pemetrexed, which may predict drug sensitivity to pemetrexed. Therefore, this trial was designed to assess prospectively the association between TS and clinical outcome of pemetrexed continuation maintenance.

Methods: The patients underwent two treatment phases: an induction phase and maintenance phase. Maintenance phase eligibility criteria included ECOG PS 0 or 1 and completion of four cycles of induction chemotherapy with radiographic evidence of partial response (PR) or complete response (CR) or stable disease (SD). Collection of tissue sample was mandatory before and after induction therapy. Real-time quantitative PCR was used to detect TS expression. TS expression level was correlated with clinical characteristic data, radiographic response, progression-free survival (PFS) and overall survival (OS).

Results: As for all 127 patients, low TS expression was associated with objective response (mean 6.85 ± 3.67, median 6.64 for responders [CR + PR] vs. mean 8.56 ± 3.69, median 8.89 for non-responders [SD + PD], P = 0.016), but no disease control (mean 7.76 ± 3.83, median 8.32 for CR/PR/PD vs. mean 8.55 ± 3.58, median 8.43 for PD, P = 0.275) after four cycles of induction treatment. As for the 67 patients who received maintenance therapy, a median score of 8.47, detected after induction treatment, was used to clarify patients as “high” or “low” TS expression. There was a significantly longer median PFS (4.7 months vs. 3.5 months, P = 0.034) and median OS (Time from random assignment: 16.4 months vs. 11.7 months, P = 0.026; Time from induction: 19.7 months vs. 14.8 months, P = 0.022) in the patients with low TS expression compared with those with high expression.

Conclusions: In NSCLC patients receiving pemetrexed continuation maintenance therapy, low TS expression is associated with improved PFS and OS.

Legal entity responsible for the study: Department of Oncology, Jiangsu Geriatric Hospital

Funding: Jiangsu Geriatric Institute

Disclosure: All authors have declared no conflicts of interest.

Final results of a phase II study of oral vinorelbine (NVBo) monotherapy in patients (pts) with advanced EGFR-positive nonsquamous non-small-cell lung cancer (NSCLC) after failure of EGFR-TKI in first line (NAOVTRIAL 2)


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Background: In advanced/metastatic EGFR-positive (EGFR+) NSCLC pts progressing after EGFR-TKIs failure in first line, single-agent chemotherapy (CT) may be offered in pts who are unfit for a platinum combination. In this study, NVBo was evaluated as monotherapy in advanced NSCLC EGFR+ pts who failed to EGFR-TKIs in first line.

Methods: Phase II, multicentre, open-label, international study. Main eligibility criteria: stage IIIB/IV NSCLC, EGFR+ prior EGFR-TKI treatment failure, Karnofsky PS ≥70, no prior CT or immunotherapy. Study treatment until progression or unacceptable toxicity: NVBo 60 mg/m² weekly for 3 weeks (first cycle), followed by 80 mg/m² weekly for subsequent cycles in absence of grade 3/4 toxicity. The primary endpoint was the disease control rate (DCR = CR + PR + SD, RECIST 1.1).

Results: 39 pts included (March 2013 - November 2014). Main pts characteristics: median age: 66.8 years (60% ≥65 years); median Karnofsky PS 90%. Adenocarcinoma 96.7% ≥3 organs involved (53.3%). All pts harboured EGFR mutation and received previous EGFR-TKI therapy: Gefitinib 73.5%, Erlotinib 16.7%, Afatinib 10%, 33.3% of pts had ≥2 comorbidities; Total number of cycles: 166 (443 doses administered); median number of cycles: 3.5 (range 1-20); median relative dose intensity: 77.6% (range 46.8-105); dose escalation was performed in 76.7% of pts; Disease control rate 63.3% (95% CI [43.8-80]) and 23.3% of patients with stable disease ≥6 months. Median time to treatment failure: 2.7 months (range 0.4-13.6). Median PFS of 3 months (95% CI [1.6-5.4]) and OS of 13.1 months (95% CI [6.1-18.5]). Grade 3/4 toxicities per pt: neutropenia 53.3%, anemia 6.7%, leukopenia 26.7%, fatigue 16.7%, nausea 3.3% and vomiting 6.7%. Three cases of febrile neutropenia reported. No grade 3/4 diarrhoea, constipation, peripheral neuropathy or alopecia.

Conclusions: NVBo as single-agent CT is a well-tolerated option in advanced EGFR+ NSCLC pts beyond failure of EGFR-TKI in first line. Its favourable tolerability profile allows a prolonged disease control in non-progressing pts.


Legal entity responsible for the study: Institut de Recherche Pierre Fabre


Funding: Institut de Recherche Pierre Fabre

Annals of Oncology
**ICFT-1003 LADIE trial: Randomized phase II trial evaluating treatment with EGFR-TKI versus EGFR-TKI associated with anti-oestrogen in women with non-squamous advanced stage NSCLC**


**Background:** The incidence of lung cancer is increasing dramatically in women and displays some specific epidemiological, radiological, clinical and pathological characteristics. Two main mechanisms emerged from recent findings in the field of lung carcinogenesis in women: the preferential involvement of the EGFR pathway and the potential impact of hormonal factors. The interaction of estrogen receptors with growth factor receptor signalling has also been shown. Preclinical data have shown that the combination of an EGFR-Tyrosine Kinase Inhibitor (TKI) with an anti-oestrogen could overcome resistance to EGFR-TKI by postponing the reactivation of the PI3K-AKT pathway through the estrogen-mediated non-genomic pathway.

**Trial design:** We launched an open-label phase II randomized trial dedicated to women with advanced stage adenocarcinoma. Patients are treated by gefitinib (250 mg/d) and fulvestrant intramuscular injection (250 mg every 3 weeks) + bevacizumab (15 mg/kg) in the EGFR mutated group (EGFR +) in first or second line setting and by gefitinib (150 mg) plus letrozole (2.5 mg) in the EGFR wild-type group (EGFR WT) in second or third line setting. Treatments are given until progression or unacceptable toxicity. Follow-up is performed in both arms every month to minimize the potential bias due to monthly fulvestrant injection. Primary objective is progression-free survival (PFS) at 3 and 9 months for EGFR WT and EGFR + patients, respectively. Secondary objectives are safety, overall survival and quality of life. Exploratory objective is biomarkers analysis. The main inclusion criteria are histologically-confirmed non-squamous NSCLC, measurable disease, no previous treatment, and prior to have a power of 80% and a two-sided significance level of 5% and planned to enroll total 214 patients. The enrollment was initiated in June 2015.

**Clinical trial identification:** NCT01556191

**Legal entity responsible for the study:** N/A

**Funding:** AstraZeneca, Ligue Nationale Contre le Cancer

**Disclosure:** All authors have declared no conflicts of interest.

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**NEJ026: Phase III study comparing bevacizumab plus erlotinib to erlotinib in patients with untreated NSCLC harboring activating EGFR mutations**


**Background:** Development of treatment for EGFR-mutated non-small-cell lung cancer (NSCLC) had been focused on monotherapy of gefitinib, erlotinib, or afatinib. However, more than half patients treated with EGFR-TKI monotherapy experience recurrence or progression of disease within a year. Some different strategies have been expected to overcome this efficacy limitations of EGFR-TKIs. One of these strategies is combination of EGFR-TKIs and VEGF inhibitors. A phase II study named JO25567 comparing between erlotinib alone and erlotinib with bevacizumab as first-line therapy in patients with advanced non-squamous NSCLC harboring EGFR mutations was conducted in Japan. This study showed that the combined treatment had extremely prolonged progression free survival as a primary endpoint than the monotherapy (Hazard ratio 0.54, p = 0.0015). Consequently, we conducted a phase III study comparing combination with erlotinib plus bevacizumab with erlotinib monotherapy.

**Trial design:** Chemotherapy-naive patients with advanced non-squamous, EGFR-mutant NSCLC are randomly assigned to receive either erlotinib (150 mg) (E arm) or a combination with bevacizumab (150 mg) plus bevacizumab (15 mg/kg) (EB arm) intravenously every 3 weeks. The double of platinum plus pemetrexed in E arm and the triple of platinum, pemetrexed, and bevacizumab in E arm are recommended as second-line therapy. Status of EGFR mutations in plasma samples are analyzed routinely from pretreatment of the first-line therapy until PD of the second-line therapy. The primary endpoint is PFS. Secondary endpoints are OS, response, safety, and patient oriented outcome. Exploratory endpoints are duration from initiation of first-line treatment to PD of second-line, detection rate of plasma EGFR mutations, association between status of plasma EGFR mutation and efficacy of 1st or 2nd line treatment, and OS analysis combined with the JO25567 study. We hypothesized that hazard ratio of PFS is 0.63. We estimated that 147 events would be needed for the study to have a power of 80% and a two-sided significance level of 5% and planned to enroll total 214 patients. The enrollment was initiated in June 2015.

**Clinical trial identification:** UMIN000017069

**Legal entity responsible for the study:** N/A

**Funding:** Chugai pharm.


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**Design of a phase II trial comparing tepotinib of gefitinib with cisplatin + pemetrexed in EGFR inhibitor-resistant, c-Met+ NSCLC**


**Background:** The phase IIb part of this trial established a recommended phase II dose for tepotinib of 500 mg/day for use in combination with gefitinib for the treatment of patients (pts) with gefitinib-resistant, locally advanced/metastatic c-Met+ NSCLC. The combination was well tolerated with evidence of antitumor activity, particularly in...
Legal entity responsible for the study: N/A
Funding: AstraZeneca R&D
Disclosure: All authors have declared no conflicts of interest.

**ALTA-1L: ALK in lung cancer trial of BrigAltinib in 1st line**: A randomized, phase 3 trial of brigatinib (BRG) versus crizotinib (CRZ) in tyrosine kinase inhibitor (TKI)-naive, advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC)

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Background: The investigational oral ALK inhibitor brigatinib BRG has potent preclinical activity against rearranged ALK and thus the ALTA-1L trial. In phase 1b study, BRG showed promising clinical activity, both systemically and in the brain, in ALK+ NSCLC patients (pts), including those with prior CRZ therapy and those who were CRZ-naive. Based on the results of an ongoing pivotal randomized phase 2 trial exploring 2 regimens of BRG (90 mg once daily and 180 mg once daily with a 7-d lead-in at 90 mg), which demonstrated substantial efficacy in pts with CRZ-resistant ALK+ NSCLC and an acceptable safety profile, the ALTA-1L trial was designed to evaluate the efficacy and safety of BRG vs CRZ in pts with advanced ALK+ NSCLC-naive to ALK-targeted therapy.

**Trial design**: The ALTA-1L trial (NCT02737501) is a multicenter, randomized, open-label, phase 3 trial. Eligible pts (18-75 years) must have locally advanced or metastatic ALK+ NSCLC without prior TKI therapy. Pts may have received up to 1 regimen of systemic anticancer therapy in the advanced setting. Approximately 270pts will be randomized 1:1 to receive BRG (180 mg once daily with a 7-d lead-in at 90 mg) or CRZ (250 mg twice daily). Pts will be stratified by brain metastases at baseline.

The primary endpoint of this study is progression-free survival (PFS) assessed by a blinded independent review committee (BIRC). The primary analysis will be performed after 198 events are observed, with 2 interim analyses planned after approximately 50% and 75% of the total expected events. Secondary endpoints include objective response rate (ORR), duration of response, overall survival, ORR and intracranial ORR and PFS, safety and tolerability, and pt-reported outcomes. Pts randomized to CRZ are permitted to cross over to BRG (180 mg once daily with a 7-d lead-in at 90 mg) after BIRC-assessed progression. The trial was initiated in April 2016 with 150 planned sites in North America, Europe, and the Asia-Pacific region.

Legal entity responsible for the study: ARIAD Pharmaceuticals, Inc.
Funding: ARIAD Pharmaceuticals, Inc.
Annals of Oncology

is not yet confirmed whether this approach would be more or less effective than SRC in the 3rd line for ALK+ NSCLC pts who relapse after both PDC and crizotinib.

Trial design: ALUR (NCT02604342) is a phase 3 open-label randomised study in pts with advanced or metastatic ALK+ NSCLC and EGOG PS 0-2 who have had one prior line of each of PDC and crizotinib. Pts (n = 120) are randomised 1:1 to receive alectinib 600mg bid or SRC (pemetrexed 500mg/m² q3w or docetaxel, 75mg/m² q3w; at investigator’s discretion) until progression, death or withdrawal. Crossover from SRC to alectinib is permitted on RECIST progression. At the investigator’s discretion, alectinib can be continued beyond progression for patients with clinical benefit. PFI was in October 2015 and LPI is expected in Q3 2016. The primary endpoint is progression-free survival (PFS) by investigator in the ITT population. Secondary endpoints include objective response rate (ORR) and time to CNS progression in the central nervous system (CNS) for pts with measurable CNS metastases (mets) at baseline; PFS by independent review committee (IRC); ORR, disease control rate (DCR) and duration of response (DOR) by investigator and IRC; time to CNS progression, CNS DOR and DCR by investigator and IRC; overall survival; health-related quality of life; time to symptom deterioration; and safety. Pts will be stratified by ECOG PS (0 vs 1), presence of baseline CNS mets and history of CNS radiation, with caps to ensure ≥50% have baseline CNS mets and both types of CNS are equally represented.

Clinical trial identification: NCT01801111 [NP28673] and NCT01871805 [NP26761].

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: J. Wolf: Advisory Boards for AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer and Roche. C. Revil: Roche Employee and Stock Ownership. A. Koth: Employee of Roche. A. Zeaier: Roche Employee, Stock Ownership and Roche Leadership. All other authors have declared no conflicts of interest.

1291TP

Phase 1b study of crizotinib in combination with pembrolizumab in patients (pts) with untreated ALK-positive (ALK+) advanced non-small cell lung cancer (NSCLC)

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Background: Crizotinib is approved internationally for the treatment of ALK+ advanced NSCLC. However, disease progression ultimately occurs in the majority of pts, often due to the development of secondary crizotinib-resistant ALK mutations or signal transduction bypass pathways. The immune checkpoint programmed cell death 1 (PD-1) pathway can be exploited by tumors to evade immune detection. ALK+ NSCLC is associated with high PD ligand 1 (PD-L1) expression, and data from a preclinical model has suggested that combining PD-1- and ALK-targeted therapies may be beneficial (Ota et al, Clin Cancer Res 2015; Voena et al, Clin Cancer Res 2015). The anti-PD-1 antibody, pembrolizumab is approved in the US for the treatment of advanced PD-L1+ NSCLC after progression on a platinum-based chemotherapy and an approved tyrosine kinase inhibitor for those with an EGFR or ALK genomic aberration.

Trial design: The primary objectives of this ongoing multicenter study (NCT02511184) are to determine the maximum tolerated dose (MTD) of crizotinib combined with pembrolizumab (dose-finding; part 1) and the recommended phase 2 dose (dose expansion; part 2), with secondary objectives to evaluate the safety profile and antitumor activity of the combination, the pharmacokinetics of both drugs, and PD-L1 expression as a predictor of antitumor activity. Part 1 uses a modified toxicity probability interval method to determine the MTD, with a starting crizotinib dose of 250 mg twice daily on a continuous schedule and intravenous pembrolizumab 200 mg on day 1 of each 21-day cycle. Seventy patients are expected to be enrolled, with 30 dose-limiting toxicity- evaluable patients expected in part 1, including a target of 10 treated at the MTD who will also contribute to the planned 50 required for part 2. Key eligibility criteria include ALK+ advanced NSCLC, no prior systemic therapy for metastatic disease, measurable disease (RECIST v1.1), available archival tumor tissue, eligibility criteria include ALK+ advanced NSCLC, no prior systemic therapy for metastatic disease, measurable disease (RECIST v1.1), available archival tumor tissue, eligibility criteria include ALK+ advanced NSCLC, no prior systemic therapy for metastatic disease, measurable disease (RECIST v1.1), available archival tumor tissue, and safety. Pts will be stratified by ECOG PS (0/1 vs 2), presence of baseline CNS mets and history of CNS radiation, with caps to ensure ≥50% have baseline CNS mets and both types of CNS are equally represented.

Clinical trial identification: NCT02511184 [NP28673] and NCT01871805 [NP26761].

Legal entity responsible for the study: F.R. Vizcarrondo

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Disclosure: J. Wolf: Advisory Boards for AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer and Roche. C. Revil: Roche Employee and Stock Ownership. A. Koth: Employee of Roche. A. Zeaier: Roche Employee, Stock Ownership and Roche Leadership. All other authors have declared no conflicts of interest.

1292TP

Amethyst NSCLC trial: Phase 2, parallel-arm study of receptor tyrosine kinase (RTK) inhibitor, MGC26265 in patients with advanced or metastatic non-small cell lung cancer (NSCLC) with activating genetic alterations in mesenchymal-epithelial transition factor (MET)

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Background: MGC26265 is a potent, orally available, small molecule RTK inhibitor of MET that inhibits both MET signaling and MET receptor internalization. Recent preclinical studies have demonstrated that MET mutations and amplifications result in increased proliferation, survival, and migration. Alterations in MET, including mutations and/or gene amplification, occur in approximately 7% of NSCLC and function as oncogenic drivers that promote cancer development and progression. Recently, various mutations located at or near the exon 14 splice site of MET (METex14dd) have been identified and result in absence of expression of exon 14. Importantly, this non-expressed region encodes
the Y1003 CBL ubiquitin ligase regulatory binding site that is required for CBL-dependent MET degradation and signal attenuation. Absence of this receptor domain results in sustained MET signaling, which has been implicated as an oncogenic driver in a subset of NSCLC. Furthermore, in xenograft models of NSCLC where MET146del and MET amplification are putative oncogenic drivers, MGD2005 induces robust tumor regression, and confirmed partial responses have been observed in patients with MET-altered NSCLC treated with MGD2005 in the Phase 1 setting.

**Clinical trial identification:** EudraCT: 2015-002070-21; Clinical trial registry number: NCT02546633

**Legal entity responsible for the study:** Mirati Therapeutics

**Funding:** Mirati Therapeutics

**Disclosure:** J. Christensen, R. Chao, D. Faltaos: Employee of Mirati Therapeutics; A. Sandler, D. Waterkamp, S. Coleman, T. Asakawa, M. Socinski and own stock. All other authors have declared no conflicts of interest.

**Phase III clinical trials in chemotherapy-naive patients with advanced NSCLC assessing the combination of atezolizumab and chemotherapy**

**Background:** Current treatments for advanced NSCLC include platinum (plat)-based doublet chemotherapy (chemo), pemetrexed (pem), bevacizumab, targeted drugs and immunotherapy. A phase II study revealed the potential for chemo to further enhance responses to atezo with tolerable safety in pts, immune cells (IC) in patients with advanced NSCLC. A phase Ib study revealed the potential for chemo to further enhance responses to atezo with tolerable safety in pts, immune cells (IC) in patients with advanced NSCLC. A phase IIb study revealed the potential for chemo to further enhance responses to atezo with tolerable safety in pts, immune cells (IC) in patients with advanced NSCLC.

**Trial design:** Three phase III randomized, multicenter, open-label studies are assessing platinum-based chemotherapy + atezo or pem-based chemotherapy + atezo + pem as IL therapy in chemotherapy-naive pts with advanced NSCLC (Table). Pts will be enrolled regardless of PD-L1 status and must have previously untreated stage IV NSCLC. Inclusion criteria include measurable disease per RECIST v1.1 and ECOG PS 0–1, pts with untreated CNS metastases, autoimmune disease or prior immunotherapy will be excluded. Stratification factors will include sex and ECOG status. Archival tumor or biopsy sample will be obtained at screening. In Dpem130 and 131, pts will be randomized to receive atezo 1200 mg with standard plat-based chemotherapy for 4 or 6 21-day cycles, then maintenance with atezo. In Dpem132, pts will receive atezo 2100 mg q4w + plat-based chemo + pem, then maintenance with atezo + pem. Endpoints include OS, PFS, ORR, DOF, safety, PK and QOL. Tumor biopsies at RECIST v1.1 progression will be assessed to distinguish pseudoprogression/tumor-immune infiltration from actual progression and to evaluate biomarkers associated with response and immune escape.

**Table: 1294TIP**

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**Clinical trial identification:** NCT02546633

**Legal entity responsible for the study:** F. Hoffmann-La Roche Ltd.

**Funding:** F. Hoffmann-La Roche Ltd.

**Disclosure:** M. Reck: Consulting/advisory role and Speaker Bureau for Roche, Lilly, BMS, MSD, Astra Zeneca, Pfizer, Boehringer Ingelheim, Celgene. V.A. Papadimitrakopoulou: Consulting or advisory role with Genentech, Genentech. V.A. Papadimitrakopoulou: Consulting or advisory role with Genentech, Genentech. V.A. Papadimitrakopoulou: Consulting or advisory role with Genentech, Genentech. V.A. Papadimitrakopoulou: Consulting or advisory role with Genentech, Genentech. V.A. Papadimitrakopoulou: Consulting or advisory role with Genentech, Genentech. V.A. Papadimitrakopoulou: Consulting or advisory role with Genentech, Genentech.
A phase 2 study of seribantumab (MM-121) in combination with docetaxel or pemetrexed versus docetaxel or pemetrexed alone in NSCLC patients with HRG+ disease


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Background: The role of the HER3 receptor and its ligand heregulin (HRG) in the progression of multiple cancers has been well established. Seribantumab is a fully human, monoclonal IgG2 antibody that binds to the HRG domain of HER3, blocking HER3 activity. This study evaluated the activity of seribantumab + standard care (SOC) versus SOCT alone in NSCLC, breast cancer and ovarian cancer. Our secondary endpoint was correlated with HERG mRNA in four patients with HRG+ tumors. This is consistent with the hypothesis that blockade of HRG-induced phosphorylation by seribantumab can sensitize cells to SOCT impaired by HRG, improving outcomes for HRG+ patients.

Trial design: In the current randomized, open-label, international, Phase 2 study, NSCLC patients with HRG+ tumors will be prospectively selected using a HRG RNA in situ hybridization assay on a recent biopsy tissue sample. Approximately 560 patients will be screened to support enrollment of 280 HRG+ patients, who will be randomized in a 2:1 ratio to receive seribantumab plus investigator’s choice of docetaxel or pemetrexed, or docetaxel or pemetrexed alone. Patients will be wild-type for EGFR and ALK and will have progressed following one to three systemic therapies for locally advanced and/or metastatic disease, one of which must be an anti-EGFR or anti-HER2 therapy. The primary endpoint is overall survival (OS). Secondary endpoints include PFS, objective response rate and time to progression. Safety and health-related quality of life will also be assessed. The study has >80% power to detect a 33% improvement in OS (0.67), using a one-sided, stratified log-rank test at a significance level of 0.025. An interim analysis is planned when 30% of final OS events have been reported. Enrollment was initiated in June 2013. Approximately 80 sites worldwide will be open to enrollment by the end of 2016.

Clinical trial identification: Clinical Trials Registry number: NCT02387216

Legal entity responsible for the study: Merrimack Pharmaceuticals

Funding: Merrimack Pharmaceuticals

Carboplatin (Cb) plus nab-paclitaxel (PTX) versus docetaxel (D) for elderly squamous (Sq) non-small cell lung cancer (NSCLC) (CAPITAL study)


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Background: Cb + weekly PTX showed survival benefits compared with vinorelbine or gemcitabine in elderly patients with NSCLC.1 However, D alone is still one of the standard therapies for them.2 The 130-nm albumin-bound formulation of PTX (nab-PTX) has shown activity in NSCLC. Cb + nab-PTX demonstrated a significantly higher overall response rate (ORR) than Cb + PTX in patients withSq histology (41% vs 24%, p<0.001) and patients >70 years showed a significantly increased overall survival (OS) with Cb + nab-PTX versus Cb + PTX.3

Trial design: This is a randomized, multicenter, phase 3 trial to compare the efficacy and safety of Cb + nab-PTX with D for elderly patients for advanced Sq NSCLC. Elderly patients (>70 years) who have received no prior chemotherapy for advanced metastatic Sq NSCLC are randomized 1:1 to D (60 mg/m2 i.v.) on day 1 and Cb (AUC 6) on day 1 plus nab-PTX (100 mg/m2 i.v.) on day 1, 8, and 15 of each 21-day cycle. Randomization is balanced by minimization for ECOG performance status, stage, age, gender and institutes. Treatment continues until radiographic progression or unacceptable toxicity. The primary endpoint is improvement of OS with Cb + nab-PTX versus D. Secondary endpoints are to assess ORR, progression-free survival, safety and quality of life. Recruitment began in December 2015 and planned enrollment is 250 patients. 1 Quiox E et al. Lancet 2011 2 Kudoh S et al. J Clin Oncol 2006 3 Socinski MA et al. J Clin Oncol 2012

Clinical trial identification: UMIN000019843.

Legal entity responsible for the study: N/A

Funding: This study was conducted by National Hospital Organization Nagoya Medical Center, under the funding contract with Taiho Pharmaceutical Co. Ltd., Japan.

Background: Use of chemotherapy near the end of life (EOL) for solid cancer patients is usually ineffective and toxic. Data about the factors associated with its use remain scarce, especially in Europe.

Methods: We designed a nationwide, register-based study including all hospitalized patients aged ≥20 years who died with metastatic solid tumors in France between 2010 and 2013. Multivariate analyses were performed to identify patients, tumor and facility level characteristics associated with chemotherapy use. Specific sub-analyses were also computed to investigate the role of the supposed tumors’ chemosensitivity (defined by the tumors response rate to first line chemotherapy).

Results: 279,846 metastatic solid cancers were included. Chemotherapy rates near the EOL were 39.1% (last 3 month), 19.5% (last month), 11.3% (last 2 weeks). During their last month of life, 6.6% of patients started or resumed a chemotherapy regimen. In multivariate analysis, female sex (OR = 0.96, 0.93-0.98), older age (OR = 0.70, 0.69-0.71 for each 10-year increase) and higher number of chronic comorbidities (OR = 0.83, 0.82-0.84) were independently associated with lower rates of chemotherapy. Tumor chemosensitivity was positively associated with the odds of receiving chemotherapy during the last month of life (OR = 1.17, 1.14-1.20). Compared with university hospitals, patients who died in for-profit hospitals (OR= 1.40, 1.34-1.45), and comprehensive cancer centers (OR= 1.43, 1.36-1.50) were more likely to receive chemotherapy. Finally, high-volume centers and hospitals without palliative care units reported greater-than-average rates of chemotherapy near the end of life.

Conclusions: Chemotherapy rates near the EOL for metastatic solid cancers patients are high, especially in young patients, treated in high-volume centers, without palliative care unit. To decrease the aggressiveness of EOL treatments, there is an urgent need to develop early palliative care, to reinforce supportive care training for oncologist, and to implement clear EOL care guidelines.

Disclosure: All authors have declared no conflicts of interest.

Background: The ESMO-DCs had high level of PC infrastructure and provided PC access to a large proportion of patients with advanced cancer. Areas for improvement include timing of referral, clinical processes of integration and educational components.

Conclusions: The ESMO-DCs reported PC research activity in the past 3 years, with pain being the most common topic (N = 99, 71%). Most centres (>80%) perceived the ESMO-DC programme to increase their status. (>80%) perceived the ESMO-DC programme to increase their status.

Disclosure: All authors have declared no conflicts of interest.

Background: Massive cancerous ascites causes severe abdominal distention, dyspnea and appetite loss, resulting in loss of patients’ activities of daily living (ADL) and discontinuation of their cancer treatment such as chemotherapy.

Methods: To improve the symptoms, we have developed a novel cell-free and concentrated ascites infusion therapy (KM-CART) which is modified from a conventional CART approved by the Ministry of Health, Labor and Welfare in Japan. KM-CART is easier to use and can be applied for massive malignant ascites. It is performed by removing the entire volume of ascitic fluid (maximum, 27 L) and administering the recovered autologous proteins (maximum, 420g) into blood vessels by infusion.

Results: A total of 2940 patients, including 458 ovarian cancer, 457 pancreatic cancer, 441 gastric cancer, 335 colon cancer patients, and 1249 patients with other disorders, underwent KM-CART between February 2009 and March 2016. Ascitic fluid was removed to the greatest extent possible (0.8–27.0 L; mean, 6.5 L). The mean processing rate was 10.4 mL/min, and between 100 and 2500 mL (mean, 560 mL) of filtered concentrate was created and administered by intravenous infusion. Side effects consisted of only mild fever, with no serious side effects observed. In all 87 patients for whom a questionnaire survey could be conducted on both the day before and the day after KM-CART, symptom scores improved for 10 items, including abdominal fullness, respiratory discomfort, decreased appetite and gait impairment. In addition, some patients resumed chemotherapy as a result of regaining the motivation to fight disease. These patients were able to transition to their homes over the long-term. Furthermore, many cancer cells were recovered from the membrane filter washing fluid and these cells were able to be used for dendritic cell (DC) vaccine therapy.

Conclusions: KM-CART system was considered easy to use and safe, and the recovery of large volumes of autologous proteins was possible to improve general status, nutrition, and immune status, as well as subjective symptoms. In addition, the recovered cancer cells were able to be used for immune cell therapy etc.

Legal entity responsible for the study: N/A

Funding: Asahi Kasei Medical Co.Ltd

Disclosure: K. Matsuaki: Patent fee from Asahi Kasei Medical CO.,LTD. All other authors have declared no conflicts of interest.

Background: Malignant ascites (MA) - fluid within abdominal cavity due to intraperitoneal (IP) invasion by cancer cells - is a sign of advanced cancer and causes distressful symptoms such as abdominal pain and dyspnea. Aim: To determine the safety and effectiveness of interventions for MA in adults with advanced cancer.

Methods: We searched 5 electronic databases (April 2015), conducted citation searching and checked reference lists of included articles and 3 systematic reviews. We included randomised controlled trials and controlled clinical trials (RCTs / CCTs). A author screened titles/abstracts. Further screening, data extraction and quality assessment were independently conducted by 2 authors and a 3rd in cases of disagreement.

Results: 221 studies were included. MA characteristics and survival were heterogeneous. Interventions were diverse, with median treatment duration of 4 months. 15 studies evaluated paracentesis (mean, 11±5). MA volume was decompressed by 17.0±4.0 L over 8±3 days (mean, 2±1 L/day). Paracentesis-related complications were rare (mean, 0.3±0.2 events per 100 patient-weeks). The crude response rate to paracentesis was 70% (95% CI, 60-79%). A single study compared paracentesis with IP chemotherapy (2.0±1.1 L/day; mean, 5.6±1.8 L/week). Paracentesis and IP chemotherapy induced similar responses (p = 0.40). The median survival was 6.5±3.4 months (mean, 29.5±11.8 months). MA volume was 17.0±4.5 L (mean, 30.0±15.3 L) at 8±3 days.

Conclusions: Paracentesis was effective and safe for patients with MA. Paracentesis and IP chemotherapy induced similar responses. Further study is needed to identify subsets of patients who may benefit from IP chemotherapy over paracentesis.

Disclosure: All authors have declared no conflicts of interest.

References:
Results: We identified 5 studies (4 RCTs, 1 CCT), with 648 participants. When reported, age ranged between 23-92 years, 77% were women and most common primary cancers were ovarian (OC) (59%) and gastrointestinal (23%). 4 interventions were pharmacological: IP Cetuximab plus Bevazzumab did not cause adverse effects (AE) and enhanced quality of life (QoL) in MA of OC, compared to IP Cetuximab alone (1 RCT, n = 58). IP Catumaxomab when added to paincentre increased more AE (abdominal pain, pyrexia, vomiting/nausea), despite reduction in MA-related symptoms (1 RCT, n = 238). IP Cetuximab-induced AE failed to be presented by Intraperitoneal Pembrolizumab (1 RCT, n = 219). Intramucosal Long-acting (LA)-Oxotremorine did not increase AE, but had limited QoL benefit compared to placebo (1 RCT, n = 33). 1 non-pharmacological intervention, abdominal massage was safe and reduced abdominal blushing, depression and anxiety, compared to social interaction (1 CCT, n = 58).

Conclusion: Cetuximab plus Bevazzumab appears safe and effective for the management of MA in OC, Catumaxomab added to paincentre increased AE, LA-Oxotremorine appears safe but with limited effectiveness, and abdominal massage is promising. However, these findings need to be confirmed in more trials.

Legal entity responsible for the study: Systematic review for MSC in Palliative Care at KCL.

Funding: Systematic review for MSC in Palliative Care at KCL.

Disclosure: All authors have declared no conflicts of interest.

1304P Intrapерitoneal bevacizumab (Bev) for control of refractory malignant ascites. A single centre experience

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Background: Malignant ascites is debilitating for patients with advanced cancer which negatively impacts the quality of life (QoL). The therapeutic options are limited and often the goal of treatment is to target palliation of symptoms. Increased Vascular Endothelial Growth Factor might be a major cause of the formation of malignant ascites. Intraperitoneal low dose 100mg Bev could be an economical option for symptom control of refractory malignant ascites and can make cost effectiveness as compared to 400mg in other clinical studies. Aims: To analyze clinical efficacy of Intraperitoneal Bevazzumab in Patients with advanced cancer and refractory malignant ascites treated at HCG, Bangalore, from July-2014 to Jan-2016.

Methods: Patients with advanced cancer and refractory malignant ascites who had received paracentesis at least once within the past 2 weeks were subjected to intraperitoneal Bevacizumab 100mg in 100 ml NaCl 0.9% after paracentesis. During the 2 months treatment period, a minimum interval of 14d was kept between the applications of Bevacizumab. The paracentesis-free survival (ParFS), best response (BR) defined as the longest paracentesis-free period and QoL were analyzed.

Results: 29 Patients (median age 57yrs), male: Female ratio 0.93:1 received at least one dose application of the Bevacizumab and qualified for the intention to treat analysis. The most common underlying malignancy with Ascites were Ovary 34.48%, Stomach 31%. The types of ascetic fluid were Hemorrhagic 55.17%, straw /clear 24.13% and Chylous 20.68%. The median ParFS was 15 days (10-23d) and The BR was 20d (10-60). The median ParFS in patients with hemorrhagic fluid was 20d, straw/clear-14d, chyloid 10d and median BR in patients with hemorrhagic fluid was 26d, straw/clear-19d, chyloid-14 d. The median ParFS in patients with carcinoma ovary was 17d, &a stomach 11d, and median BR in patients with ca ovary was 23d, & ca stomach 15d.

Conclusions: Low dose intraperitoneal Bevazzumab is an economical option and gives better symptom control of malignant ascites especially in hemorrhagic type. Further randomized studies should be conducted and compared between 100mg and 400mg bevazzumab before routine clinical practice.

Legal entity responsible for the study: HCG, Ethical Committee

Funding: HCG

Disclosure: All authors have declared no conflicts of interest.

1303P Knowledge of pain management in patients with painful bone metastases: A multicentre randomized trial on pain education

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IP Cetuximab in patients with painful bone metastases were randomized between nurse-led tailored education regarding pain management or care as usual. A worst pain score of 2.5 on a 0-10 numeric rating scale (NRS) was one of the inclusion criteria. The primary endpoint was pain intensity. Here we report on pain knowledge in patients randomized in the education arm.

Methods: Patient characteristics, pain intensity (NRS) and patients’ thoughts regarding pain management were assessed using a structured interview. This interview took place between randomization and start of radiotherapy. Patients were asked whether they completely agreed–completely disagreed on a 5-point Likert scale with the following statements 1) cancer pain can be relieved effectively 2) pain medication should be given only when pain is severe 3) most cancer patients will become addicted to pain medication 4) it is better to give the lowest amount of pain medication, so that larger doses can be used later if pain increases 5) it is better to give pain medication around the clock than only when needed 6) non-pharmacological interventions can relieve pain? 7) patients are often overmedicated 8) use of pain medication can be changed without consulting a physician. Lack of knowledge was identified if they completely or fairly disagreed on statement 1, 5, 6 or, completely or fairly agreed on statement 2, 4, 7 or 8.

Results: 167 patients were interviewed, mean age 65 ±10 years. Mean worst pain at inclusion was 7.9 ±4.5. 52% of patients used strong opioids (WHO step 3). Most patients (59%) lacked knowledge of at least one statement (median 2, range 1-6). Lacks were found most frequently for statements 4 (69%), 2 (41%), 3 and 7 (both 28%). Patients’ knowledge was best about statements 8 (77% disagreed); 5 (74% agreed) and 1 (73% agreed).

Conclusions: Most patients lack sufficient knowledge on different topics of pain management, advocating tailored pain education.

Clinical trial identification: ZonMW 11510007 07-10-2010

Legal entity responsible for the study: N/A

Funding: KWF ZonMW

Disclosure: All authors have declared no conflicts of interest.

1304P Efficacy of Quadramet® (QUA) as treatment of painful bone metastasis: A large single-center study

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Background: QUA has been used in the management or care as usual. A worst pain score of 5 on a 0–10 numeric rating scale (VAS) (0 to 10), (ii) presence or absence of sleep disturbance related to pain, (iii) dose of analgesic medication, and (iv) answer to the following closed question “Do You think You get a benefit of treatment?”. Success of treatment was defined by a combined criterion including these 4 parameters. Results: From January 2001 to December 2012, 370 consecutive QUA treatments for painful bone met. were delivered in our department. Primary tumors were: breast carcinoma (153), prostatic carcinoma (155), lung carcinoma (27), or other cancers (35). Mean age of the pts was 65 ± 12 years. Fifty-eight percent of the pts had previous external ossseous radiotherapy. Ninety-seven percent of pts had concomitant analgesics and 61% were under diprophosphonates. Pts described benefit at D30 in 50%, 48%, 29%, and 33% of cases for breast, prostate, lung and others cancers, respectively (p = 0.12). Pts described benefit at D30 in 62%, 58%, 29%, and 33% of cases for breast, prostate, lung and others cancers, respectively (p= 0.12). Pts described benefit at D30 in 62%, 58%, 29%, and 33% of cases for breast, prostate, lung and others cancers, respectively (p= 0.12).

Conclusions: QUA therapy is an effective supportive treatment in pts suffering from bony met., especially in breast and prostate cancer pts.

Legal entity responsible for the study: Centre Oscar Lambret

Funding: Centre Oscar Lambret

Disclosure: All authors have declared no conflicts of interest.

1307P Use of treatments of questionable benefit in hospitalized patients with metastatic gastric or esophageal cancer near the end of life. A country-wide, register-based study

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Background: The benefit of life-prolonging treatments in terminally ill cancer patients is debated. Little is known, however, about the aggressiveness of care in patients with metastatic esophagus or stomach cancer.
Methods: Register-based study in France, including all hospitalized adults (≥20 years) who died as the result of metastatic esophageal or gastric cancer between 2010 and 2013. The receipt of chemotherapy and the use of artifical nutrition during the last 3 months of life were defined as primary outcomes.

Results: 4,035 patients with metastatic esophageal cancer and 10,423 patients with metastatic gastric cancer were included (n total = 14,458). Overall, 47.6% of patients received chemotherapy in their last 3 months of life, with a significant decrease over time (from 35.9% during the third month before death to 7.9% in the final week of life). In contrast, the receipt of artificial nutrition rose from 9.4% to 16% over the same period of time. This increase in the use of artificial nutrition was observed for both esophagus and stomach cancer, across all age-groups, and regardless of the number of chronic comorbidities (p = 0.001 for trend). During the last week before death, the likelihood of receiving artificial nutrition decreased with age (adjusted OR = 0.88, 95% CI = 0.77-0.94 for each 10-year increase in age), and was significantly higher for patients with esophageal cancer compared with gastric cancer (adjusted OR = 1.25, 95% CI = 1.13-1.37). In addition, 3.5% of patients received invasive ventilation during the last month before death (5% of patients with esophageal cancer and 3% of patients with gastric cancer, p = 0.001). 6% of patients eventually died in Intensive Care Units, and only 12.6% died in Palliative Care Units.

Conclusions: Our study shows that hospitalized patients with metastatic esophageal or gastric cancer are likely to receive treatments of questionable benefit near the end of life. Interventional studies focusing on patient reported outcomes are needed to assess the clinical benefit of artificial nutrition for patients with terminal cancer.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
End of life (EOL) chemotherapy (CT) in gastro-intestinal (GI) cancer patients (pts): A retrospective AGEO study


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Background: The use of CT during the EOL is poorly studied, with no dedicated study to GI cancer pts. Here, we report results of a retrospective study in this specific population, in the aim to analyze the factors associated to CT use within 3- and 1-month before death.

Methods: All pts that died from a GI cancer in 10 French tertiary care hospitals during 2014 were included in this retrospective cohort. Clinical (primary tumor, treatment history, performance status) (PS), sociodemographic (age, sex, place and date of death) and biological (albumin level) data were collected and compared between pts receiving or not CT within 3- and 1-month before death. Overall survival (OS) defined as the time from diagnosis until death from any cause, was estimated using Kaplan Meier method. Uni- and multi-Cox regression models were performed to estimate hazard ratio of all baseline variables with its 95% confidence interval (CI).

Results: 437 pts were included in this study. All had a metastatic GI cancer (colorectal: 36.2%, pancreas: 28.4%, gastric: 10.3%, esophageal: 9.8%, cholangiocarcinoma: 8.2%, hepatocarcinoma: 3.9%, others: 3.2%). Among them, 203 pts (46.9%) received CT within 3-months before death and 144 (33.0%) did not, and 121 pts (27.7%) received CT within 1-month before death (516 (72.3%) who did not. Pts receiving CT within 3-months before death were significantly younger (median age: 65.5 vs 72.8 years, p < 0.0001), with a better PS (PS 0 or 1: 53.9 vs 28.5%, p < 0.0001) and higher albumin level (median: 32.8 ± 3.1 vs 30.1, p < 0.048), higher number of previous line of CT (median of line number: 2 vs 1, p < 0.0001). No difference in OS was found between the 2 groups at 3-months before death. Pts receiving CT within 1-month before death had the same characteristics than the 3-month group and were more likely to die in medical intensive care unit than in palliative care unit (81.8 vs 64.2%, p < 0.01).

Conclusions: In GI cancer units, CT is given within 3- and 1-month before death, in two and one third of patients, respectively. Analysis of survivals together with a score aimed to drive treatment discontinuation decision will be presented at the meeting.

Legal entity responsible for the study: Geraldine Perkins

Funding: AGEO

Disclosure: All authors have declared no conflicts of interest.
Antineoplastic therapy near the end of life: A retrospective analysis of the clinical practice in oncological adult patients

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Background: Around 70% of oncological patients with disseminated disease are receiving chemotherapy with palliative intent. However, giving palliative chemotherapy near the end of life, is a balance between clinical benefit and potential harm in terms of side effects. Treatment interruption in the final stages of life is considered a factor determining good clinical practice. Earle et al. (J Clin Oncol 2004) define the concept of treatment non-aggressiveness as chemotherapy administration below 10% during the last 14 days of life.

Methods: A retrospective observational study was conducted in a tertiary hospital. The study included all oncological patients with advanced cancer who died between January 2014 and August 2015. For descriptive analysis, the statistical program SPSS was used.

Results: Between January 2013 and August 2015, 452 patients with oncological advanced disease and palliative follow-up care died. 67% (n = 306) of these patients had received antineoplastic treatment. These were the patients that were analyzed. The median age of patients was 64.5 years (range 17-86), 66.7% (n = 208) were male and 33.3% (n = 104) were female. The most frequent tumors suffered by patients were 30.4% (n = 95) breast cancer and 14.1% (n = 44) colorectal cancer. The median number of treatment regimens received was 2 (range 1-9). There were 69 patients who received more than three different regimens (22.5%). 57.8% (n = 177) of the patients maintained the antineoplastic treatment during the last 3 months before death. 20.6% (n = 63) of the patients received chemotherapy in the last 30 days of life, and 10.1% (n = 31) received chemotherapy in the last 14 days of life. 78% (n = 237) of the patients died at hospital, and 22% (n = 67) died at home.

Conclusions: The use of chemotherapy during the last period of life of cancer patients is a controversial issue. The outcomes of our study show that the proportion of patients in the oncology department who received chemotherapy at the last stage of life is similar to that observed by Earle et al. We need more scientific evidence to consolidate data allowing us to establish criteria for the selection of patients who may benefit from receiving antineoplastic treatment.

Legal entity responsible for the study: University College London Hospitals

Funding: UCL/UCLH-NIHR Biomedical Research Centre. M.L. is also supported by Cancer Research UK and Prostate Cancer Foundation.

Disclosure: H. Payne: Educational grants from Astellas and Jansen. M. Linch: Educational and research grants from Bayer, Sanofi, BMS. All other authors have declared no conflicts of interest.

Supportive home care service: A home-based simultaneous care intervention

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Background: An increasing amount of scientific evidence has confirmed the utility for cancer patients, in terms of quality and quantity of life, performance of therapeutic results, and gradual transition of care, of a simultaneous care approach. In a period of human and financial resource constraints innovative forms of cooperation between oncologists and palliative care providers are needed.

Methods: The Oncology Department in the Florence Health District with the support of the Tuscany Tumors Association, a non-profit organization, has conducted, from March to December 2015, a pilot project to test the feasibility of a Supportive Home Care Service, a dedicated home-based service for the prevention and treatment of severe cancer symptoms, and of the side effects and toxicities secondary to palliative cancer therapies. Home care was guaranteed by a highly qualified staff, and was available 24 hours a day, every day of the year.

Results: A total of 28 patients, median age 75 years (range 46-85), affected by advanced solid tumors were enrolled. The majority of patients had metastatic disease (82%), and 33.3% (n = 104) was female. The most frequent tumors suffered by patients were 30.4% of the total) as the ratio between the number of admissions and the number of patients). Thirteen patients (46% of the total) had already died. 99.9% of them had incurable cancer. 60% of them were treated at APACD inpatient unit, 23.5% at outpatient clinic and 15.9% were advised by specialist palliative care consultation team. The mean time of palliative care service referrals for the whole group and period was 54 days. When we compared the three triads between each other we observed a small trend to earlier referrals (2007-2009: 42days, 2010-2012: 51 days and 2013-2015: 61 days).

Conclusions: We observed no referrals in the last triad of the APACD existence at our institutions comparing first and second triad, still the referrals are later in the illness trajectory.

Legal entity responsible for the study: Oncology Institute of Lubljana

Funding: Oncology Institute of Lubljana

Disclosure: All authors have declared no conflicts of interest.

Percutaneous biliary drainage in malignant obstructive jaundice: Is it really necessary for all patients with malignant obstructive jaundice?

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Background: Malignant obstructive jaundice (MOJ) in cancer is due to liver metastasis and/or biliary duct compression. Percutaneous biliary drainage (PBD) is a palliative
Conclusions: Coexisting COPD was associated with worse survival outcomes in patients with advanced NSCLC. Our analysis indicated that COPD treatment might have potential to salvage the prognosis of such patients.

Legal entity responsible for the study: Kyoto University

Funding: Kyoto University

Disclosure: All authors have declared no conflicts of interest.

Efficacy and tolerability of transdermal fentanyl versus oral prolonged-release oxycodone/naloxone in patients with moderate to severe cancer pain: A propensity analysis comparison

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Background: In cancer patients treated with opioids, both transdermal Fentanyl (TF) and oral PR Oxycodone-Naloxone (OXN) have been found effective in reducing pain, with less constipation in comparison with other opioids. No direct comparison is available between TF and OXN.

Methods: Consecutive cancer patients with moderate to severe cancer pain and naive to WHO-III strong opioids enrolled in a two prospective 28-day studies (NCT01809106, NCT02293785) and receiving TF or OXN were selected; to adjust for bias inherent to heterogeneity and decision about their opioid therapy, we performed a propensity score analysis by multivariable logistic regression. Outcome measures included analgesic efficacy over time [worst and average pain NRS intensity decrease (APID), analgesic response (APID >30%), daily opioid dosage (morphine-equivalent mg), daily opioid dose increase and rate of abnormal (>5%) escalation index] and safety profile as premature switch to other analgesics, constipation and other adverse events (AEs).

Results: 124 TF and 173 OXN patients were included in the comparative analysis (age 68.3±10.3; female 41.8%; average pain intensity at baseline 6.2±1.3). The 28-day APID were similar between TF and OXN (worst -45.3 vs -43.3%; average -53.9 vs -52.0%; both NS); response rates were also comparable (75.9% TF vs 82.5% OXN, NS), indicating similar analgesic efficacy. However, different daily MEQ dosages were used both at baseline (53.4 TF vs 25.5 mg OXN, p<0.001) and after 28 days (111.0 vs 44.1, p<0.001). A dose escalation >5%/daily was markedly less common after OXN (20.4% vs 35.9% TF; p=0.002), indicating less need of therapy adjustment. Premature switch (12.6% in TF vs 11.2% OXN, NS) and constipation (28.9% TF vs 26.1% OXN, NS) were comparable; other AEs were slightly more common after TF (51.2% vs 41.9% OXN, p=0.11).

Conclusions: In this propensity analysis of patients with moderate-severe cancer pain, OXN showed similar analgesic efficacy compared to TF, despite strikingly lower daily dosages and need of drug escalation, suggesting less mid-term tolerance with OXN in cancer pain.

Clinical trial identification: NCT01809106, NCT02293785

Legal entity responsible for the study: IRCCS-Istituto di Ricerche Farmacologiche Mario Negri

Funding: IRCCS-Istituto di Ricerche Farmacologiche Mario Negri

Disclosure: All authors have declared no conflicts of interest.

OncoSTRIP for optimizing pharmacotherapy in elderly oncology patients with polypathy

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Background: Polypharmacy in geriatric oncology is associated with more treatment related toxicity and a higher frequency of drug drug interactions with oncology drugs.

procedure. Prognostic & predictive factors are needed for selection of the cancer patients who will get more benefit from PBD in MOJ. We evaluated cancer patients (CP) who had PBD for MOJ for clinico pathological features (CPF) & survival outcomes besides potential predictive markers for PBD.

Methods: 110 CP who had PBD for MOJ between 2010 & 2016 were evaluated retrospectively. The correlation between biochemical values, CPF (extrahepatic metastasis (EM), obstruction cause (OC), stent localization) & total bilirubin (TB) was evaluated by ROC analysis. The CP were analyzed according to TB after PBD (groups A: normal (<1.2 mg/dl), B: modest decrease (>1 mg/dl or 20% decrease), C: stable/ increase.

Results: Median age was 60 (28-82) years. 57 were male. In univariate analysis, EM & OC were significant factors with concordance to biochemical values. Albumin (p = 0.007, OR: 2.5, 1.25-17.1), LDH (p = 0.04), OR: 2.5, 1.06-6.2) & OC (p = 0.019, OR: 4.3, 1.2-9.9) remained significant in multivariate analysis. The CP were grouped according to these risk factors (RF) groups 1 (22.7% no RF), 2 (64.5% 1-2 RF), 3 (12.7% >3 RF). TB normalization & OS after PBD are shown in table 1. Stenting proximal to choledoc had better TB normalization (44.7% vs 17.6%, p = 0.006).

Chemotherapy rates were as 60% for group A, 36.8% for group B & 21.9% for group C (p = 0.084). 6-months OS was 41.3% for patients receiving chemotherapy & 17.7% for others (p <0.001).

Conclusions: Basal higher LDH, lower albumin & obstruction due to more liver metastasis are poor prognostic factors for PBD. Higher TB, stenting proximal to choledoc & EM have poor outcomes. PBD for MOJ in cancer should be considered for high risk groups, not all patients.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Survival impact of treatment for chronic obstructive pulmonary disease in patients with advanced non-small cell lung cancer

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Background: The prognosis of patients with advanced non-small cell lung cancer (NSCLC) and coexisting chronic obstructive pulmonary disease (COPD) is uncertain. In addition, no previous studies have examined whether treating COPD improves the prognosis of such patients.

Methods: We focused our retrospective analysis on advanced NSCLC patients who had received chemotherapy at Kyoto University Hospital between 2007 and 2014. The association between COPD treatment and overall survival (OS) was assessed using the log-rank test and Cox logistic regression models adjusted for age, sex, smoking, chemotherapy, the percentage forced expiratory volume in 1 second (%FEV1.0), and COPD treatment.

Results: Of the 358 patients enrolled, 104 had COPD (COPD group) and 254 did not (non-COPD group). Thirty-seven patients in the COPD group had received COPD treatment. The median OS period was 325 days in the COPD group and 510 days in the non-COPD group (p = 0.001). Among the COPD group, the patients that had received COPD treatment exhibited a significantly longer median OS period (307 days vs. 247 days, p = 0.0211). Multivariate Cox regression analysis (Table) showed that COPD treatment has a positive prognostic impact in patients with advanced NSCLC (HR: 0.425, p = 0.0006).

Table: 1319P

<table>
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<th>Group A (%)</th>
<th>Group A (%)</th>
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<td>Total bilirubin (mg/dl)</td>
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</table>
Polypharmacy assessment has been introduced as part of care of several high risk patient groups, however experience in oncology patients is limited and no standardized method is available. We aimed to develop a polypharmacy assessment method that can be integrated in routine care of geriatric oncology patients to improve quality of life and compliance, and to decrease toxicity and costs. 

Methods: Patients ≥65 years and with ≥5 chronic medications that visited our outpatient oncology clinic were offered a polypharmacy assessment by a clinical pharmacist. The polypharmacy assessment was based on the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method and consisted of a polypharmacy anamnesis with the patient, a subsequent polypharmacy analysis, and an optimized polypharmacy treatment plan that was provided to the oncologist. In parallel, a geriatric assessment was performed using ACE-27, ECOG and G8 scoring systems to score comorbidity, performance and frailty, respectively. 

Results: The OncoSTRIP polypharmacy assessment is now integrated as part of routine care of geriatric oncology patients in our hospital. At the time of the first analysis, 24 patients (17 male and 7 female, mean age 74.3 years) had undergone a polypharmacy assessment. The mean number of chronic medications, oncology medications, supportive medications and total medications was 8.0 (range 4-14), 2.3 (range 1-5), 2.4 (range 0-6) and 12.7 (range 6-21), respectively. Polypharmacy treatment optimization was proposed for 19 (79%) of patients, with a total of 26 suggested pharmacotherapeutic modifications. Mean time spent per patient was 53 minutes. 

Conclusions: Polypharmacy assessment of geriatric oncology patients identifies many possible optimizations in pharmacotherapy. The OncoSTRIP method can be integrated in routine care of geriatric oncology patients. Supported by a grant from the Dutch Cancer Society. 

Legal entity responsible for the study: N/A 

Funding: Dutch Cancer Society 

Disclosure: All authors have declared no conflicts of interest.

1323P Palliative medicine in Iran
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Background: It is well known that palliative care is a necessity in cancer patients, as early on as the time of diagnosis. Palliative care for cancer patients is rather new in Iran and has a history of less than 8 years. 

Methods: Here we give an overview on the status of palliative care in Iran. We also present the demographics of our patients in the largest palliative care unit over the last two years. 

Results: Iran has a population of around 80 million people and, according to the official cancer registry, a yearly cancer incidence of around 100 thousand. We currently have around 8 active palliative care units for cancer patients and one palliative care ward in Iran, all run by charities. In these palliative care units, we have oncologists, palliative care specialists, pain specialists, psychologists, spiritual care specialists, social workers and dieticians. A total number of 3677 patients, of whom 3277 (89%) had a primary spinal tumors, 23 metastatic). The most common origins of the metastatic primary cancer, 339 (10%) had hematologic malignancies, 312 (10%) had esophageal or gastric cancer, 311 (10%) had colorectal cancer, 105 (3%) had a cancer of the CNS, 101 (3%) had lymphoma, 93 (3%) had renal cancer, 87 patients (3%) had ovarian cancer, 81 (2%) had lung cancer, 54 patients (2%) had prostate cancer and 50 (2%) had pancreatic cancer. The other 40% of the cancer patients had either less frequent cancers or their exact cancer site was not recorded.

Conclusions: Iran, like many other countries, needs many more palliative care units. As palliative medicine is not financially lucrative, charities play a major role in setting up, maintaining and expanding these units. 

Legal entity responsible for the study: Ala Charity  

Funding: Ala Charity  

Disclosure: All authors have declared no conflicts of interest.
prevention and screening

A survey among breast cancer specialists on the low uptake of breast cancer preventive therapy with tamoxifen or raloxifene

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Background: Despite the strong evidence of efficacy and FDA indication, breast cancer chemoprevention with tamoxifen or raloxifene has found so far little uptake in clinical practice. This survey aims to evaluate the knowledge, attitudes and beliefs of expert physicians regarding the reasons of this low uptake.

Methods: In late 2012 and early 2013 a self administered questionnaire was given during breast cancer meetings in Italy and Switzerland or submitted electronically to the breast cancer European School of Oncology alumni. The questionnaire included 4 personal questions (gender, age, country of work and specialty) and a 5-point (from very important to unimportant) 10-item Likert Scale with the following, here summarized, statements on the reasons of low uptake: 1. no demonstrated mortality effect, 2. Fear of side effects, 3. lack of reliable surrogate markers, 4. unclear who is the appropriate physician, 5. risk model is difficult, 6. lack of medical knowledge, 7. prevention of otherwise curable cancer, 8. drugs have poor commercial interest, 9. off-label in EU, 10. waiting results of Aromatase Inhibitors trials.

Results: Of the 246 surveys collected, 219 were filled in. In the 168 surveys with demographic information there were 88 female and 81 male, 110 European and 58 non European, 113 oncologist and 55 non-oncologist physicians. In the overall response on 219 physicians, the off-label use of drugs (17%), the lack of mortality data (15%), the lack of knowledge among physicians (13%), poor commercial interest in these drugs (12%) and the fear of side effects (11%) were the top five “very important” reasons for the low uptake. In subgroup analysis the top statement was: i) the off-label use for physicians ≥ 45 years (47%), ii) the lack of mortality data for those < 45 years (39%) and non-oncologists (39%), iii) the fear of side effects for oncologists (53%) and European physicians (56%).

Conclusions: This survey, which is the first to assess the attitudes of experts physicians towards breast cancer chemoprevention, highlights the complexity of this field and, coupled with the known barriers among potentially eligible women, may help to identify strategies to increase chemoprevention uptake.

Legal entity responsible for the study: E.O. Ospedali Galliera di Genova

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A ‘one stop cancer screening shop’, a way of improving screening participation rates?

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Background: It is well established that cancer screening programs can reduce morbidity and mortality, however, research demonstrates that screening programs are underutilised by the target populations. Therefore the aim of this study was to investigate enablers and barriers to cancer screening and how screening participation may be improved.

Methods: Participants who were randomly selected from northern and western suburbs of Adelaide, Australia answered online or paper based questionnaires about health issues and service utilization. Data were collected from 10th August-20th December 2015, weighted for selection probability, age and sex and analysed using SPSS®.

Results: 2,895 questionnaires were sent, with 1,562 returned (54%). Respondents included 754 males and 808 females with a mean age of 54.1yrs (+ 15.2). Current cancer screening participation included cervical 34.4% (CI 32.1-36.8), bowel 34.1% (CI 31.7-36.4), breast 28.7% (CI 26.5-31.0) and prostate, 17.4% (CI 15.6-19.4). Commonly cited reasons for screening participation included: preventing sickness (CI 36.1%, 33.2-39.0), maintaining health (CI 51.9%, 48.5-55.3), free program (CI 30.9%, 28.2-33.6) and family history of cancer (20.9% (CI 18.7-23.4)). The most common screening barrier was irrelevance of screening to the person (CI 20.8%, 17.2-24.8), with a small proportion stating time (CI 6.9%, 4.9-9.7) and cost restraints (CI 3.5%, 2.3-5.7). Ninety three percent (CI 91.7-94.2) of respondents thought cancer screening was beneficial, with the majority (85.3%, CI 83.4-86.9) supporting the concept of different types of screening being provided at the one site.

Conclusions: Participation rates in individually offered cancer screening programs (colorectal, breast, cervical) remain low. The enablers and barriers to screening participation cited in this study are in concert with those in the published literature, however, an overwhelming percentage of respondents would support a combined cancer screening service. Offering a combined co-located service - a ‘one stop cancer screening shop’ has the potential to address barriers to screening (such as time constraints), improve participation rates and maximize utilization of public health resources.

Legal entity responsible for the study: SA Health, The University of Adelaide, the University of South Australia, The Queen Elizabeth Hospital, the Lyell McEwin Hospital and the Institute of Medical and Veterinary Science

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Disclosure: All authors have declared no conflicts of interest.

HIV1-positive men who have sex with men (HIV1-MSM) knowledge and attitudes towards anal cancer screening: A cross-sectional study

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Background: Despite combined antiretroviral therapy, risk of anal cancer is eighty times higher in HIV1-MSM than in general population. Although no international consensus exist for routine screening of anal cancer for HIV1-MSM, guidelines in most western countries include at least digital anal examination. Participation may be beneficial to diagnose high grade squamous intraepithelial lesion. This monocentric cross-sectional study aims to describe HIV1-MSM knowledge and attitudes towards anal cancer screening (ACS).

Methods: All adult patients (pts) HIV1-MSM who went to the Hôpital Européen Georges Pompidou in Paris (France) for a consultation were invited to complete a self-administered questionnaire about their knowledge regarding ACS and their previous experience. We explored factors associated with previous screening uptake, among patients familiar with ACS, with multivariable logistic regression.

Results: Among an active list comprising 1019 pts HIV1-MSM, 410 completed the questionnaire between June 2013 and January 2016. Median age was 50 years (IQR, 42.5-57.5) and median time from HIV diagnosis was 14.2 years (IQR, 6.9-23.1). HIV viral load was < 20 copies/mL for 381 (92.9%) pts and median CD4-cell count was 685 cells/μL (IQR, 531-905). Most of the pts were aware of the existence of ACS (n = 335, 81.7%) and among those 191 (57%) had already took a screening test. Absence of screening (n = 144, 43%) was most often explained by lack of time (28.5%) and lack of information (28.5%). Among pts familiar with ACS, those older than 50 years (versus < 50 years, ORa =2.3, 95% CI 1.2-4.5, p = 0.017) and those informed by healthcare providers (versus other information sources, ORa =8.5, 95% CI 2.6-33.6, p = 0.001) were more likely to have already been screened.

Conclusions: Although 82% of the HIV1-MSM were familiar with ACS, only 57% of them have already taken a screening test. Information by physician seems the best intervention to promote the screening. Encouraging physicians to inform HIV1-MSM pts on anal cancer may improve ACS uptake. Moreover, more detailed information and better accessibility of screening centers should help improve screening rate.

Legal entity responsible for the study: APHP

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Disclosure: All authors have declared no conflicts of interest.
Opinion on cancer screening: Impact on prescription and participation rates

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Background: The aim of the EDIFICE surveys is to improve insight into screening programs in France. We hypothesized that individual opinions may affect physicians’ and laypersons’ attitudes toward prescribing or participating in screening, respectively; we assessed physicians’ and laypersons’ opinions, focusing on colorectal (CRC), breast (BC), cervical (CC), prostate (PC) and lung (LC) cancer screening.

Methods: The 4th nationwide observational survey was conducted by phone interviews using a quota method. A representative sample of 1463 individuals with no history of cancer (age 49-75 y; 726 men [m], 737 women [w]) was interviewed from 12 June-10 July 2014. A mirror survey on a representative sample of 301 physicians (201 general practitioners [p] m, 101 m, 70 w) and 100 oncologists (60 m, 35 w) was conducted from 9 July-8 August. We analyzed replies stating screening to be more reassuring than worrying.

Results: In general, screening was more reassuring than worrying, more so for physicians than for laypersons (CRC 65% vs 51%, CC 74% vs 62%, PC 59% vs 43%, P < 0.05; BC 71% vs 63%, LC 45% vs 43%, not significant [NS]). Among physicians, oncologists tended to consider screening as more reassuring than worrying (BC 83% vs 66%, P = 0.05; CRC 70% vs 63%, P = 0.05; CC 83% vs 70%, NS) except for PC (49% vs 64%, P = 0.05) and LC (44% vs 45%, NS). GP declared they would prescribe screening regardless of their own opinion, i.e., whether they believe it to be reassuring or worrying (CRC 81% vs 82%, respectively, BC 93% vs 88%, CC 21% vs 15%, NS), except for PC (80% vs 64%, P < 0.01). Participation rates tended to be higher among reassured than worried laypersons (CRC 71% vs 48%, PC 63% vs 36%, P = 0.05 and BC 98% vs 96%, CC 99% vs 98%, LC 12% vs 10%, NS).

Conclusions: Physicians tend to be more reassured by screening than laypersons more so than GP, with the exception of PC screening. The official guidelines for CRC and BC screening are a good setting for GP’s medical practice. The most widely used screening programs (CRC, BC, PC) enable GP to make objective prescriptions, regardless of individual opinions. In the absence of guidelines (PC), prescription rates are correlated with physicians’ confidence in screening. Reassurance in screening has a positive impact on laypersons’ participation rates.

Legal entity responsible for the study: EDIFICE surveys are funded by Roche

Funding: EDIFICE surveys are funded by Roche

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Immunohistochemical biomarkers for risk stratification of neoplastic progression in Barrett esophagus

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Background: Barrett’s esophagus (BE) is the precursor lesion of esophageal adenocarcinoma (EAC). None of the current clinical, endoscopic criteria are able to accurately predict which patients will progress from BE to EAC. Immunohistochemical (IHC) biomarkers can be applied to intact histological morphology and are relatively easy applicable in daily practice. This study aimed to provide a systematic review and meta-analyses of all published studies on IHC biomarkers as predictors of neoplastic progression in BE.

Methods: MEDLINE, EMBASE, Web of Science, CENTRAL, Pubmed publisher, and Google scholar were searched. All studies on IHC biomarkers in BE progression were included. Two authors independently extracted data. Meta-analyses were performed for biomarkers studied more than once. Pooled estimates of effect were calculated. If enough studies were present, sensitivity analyses and sub-analyses were performed. Sub-analyses were performed to investigate whether IHC biomarkers had a predictive value independent of the presence of LGD.

Results: IHC biomarkers studied more than once were p53, Cyclin A, Cyclin D, and p53. p53 was included in 12 studies, which included 2032 patients, amongst which 372 cases. The meta-analyses showed aberrant p53 IHC staining was significantly associated with the risk of neoplastic progression in BE patients with an OR of 4.15 (95% CI 1.95 to 8.81). A sub-analysis stratifying for the presence or absence of LGD showed that aberrant p53 IHC staining was associated with neoplastic progression with an OR of 4.15 (95% CI 2.36 to 7.21). This association was confirmed for both non-dysplastic BE, and BE with low grade dysplasia. Of the other IHC biomarkers, Cyclin A (OR 1.34, 95% CI 0.62 to 2.79), Cyclin D (OR 1.87, 95% CI 0.97 to 3.79), and A0L, only A0L appeared to be able to predict neoplastic progression in BE patients with an OR of 3.04 (95% CI 2.05 to 4.49).

Conclusions: In conclusion, p53 is the most studied IHC biomarker for neoplastic progression in patients with BE. Aberrant p53 IHC is significantly associated with an increased risk of neoplastic progression in BE patients, which appears to be independent of dysplasia grade.

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Disclosure: All authors have declared no conflicts of interest.

A logistic regression model based on tongue image information for prediction precancerous lesions and early stage esophageal cancer in China

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Background: China is an esophageal cancer high incidence country, with more than 50% esophageal cancer case of the world. Screening and diagnosis of precancerous lesions and early stage cancer are main measures of decreasing incidence rate and mortality rate.

Methods: High-risk population (40-69 years old) in Cixian a high risk area of esophageal cancer was screened, and 3053 cases were included. They were divided into 3 groups: normal group, esophageal neoplasia low-level group and esophageal neoplasia high-level group, according to pathology and electronic gastroscopic diagnosis. Diagnostic testing lingual image collection system (DSII-B) was used and tongue image were collected, including tongue color, coating color, fur character, tongue shape, local ecchymosis, et al. Difference of tongue image information was analyzed, related clinical variants were analyzed by multi-factor logistic regression.

Results: Incidence of local ecchymosis in tongue image was 1.58% (45/2840) in normal group, 2.98% (4/134) in esophageal neoplasia low-level group and 6.32% (5/79) in esophageal neoplasia high-level group. Significant difference was found in 3 groups (P < 0.05). Logistic regression analysis showed that age, male, red tongue, tongue local ecchymosis, yellow and white coated tongue were risk factors for precancerous lesions and early stage esophageal cancer. Logistic regression model was established and this model had diagnostic specificity (80.35%), sensitivity (63.41%) and total coincidence rate (79.51%) for early esophageal cancer screening.

Conclusions: Red tongue, tongue local ecchymosis, yellow and white coated tongue were risk factors for precancerous lesions and early stage esophageal cancer. Multi-factor (including tongue image information) logistic regression model has clinical value of prediction precancerous lesions and early stage esophageal cancer. Legal entity responsible for the study: China-Japan friendship hospital

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Disclosure: All authors have declared no conflicts of interest.

Duodenal neoplasm in screening esophagogastroduodenoscopy

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Background: It is difficult and often impossible to see the whole duodenum with esophagogastroduodenoscopy (EGD) technically. It seems sufficient for most of the EGD screening programs to search around the first and the second portions of the duodenum including duodenal papilla for duodenal neoplasms because other duodenal portions are believed to have rare neoplastic lesions.

Methods: The data of the EGD screening program from June 2012 through April 2016 at Otsu Memorial Hospital (OMH) in Japan was reviewed. All duodenal neoplasms detected in the EGD screening program were analyzed to reveal their characteristics.

Results: 17,449 individuals were enrolled in EGD screening program of OMH during the above period. Thirteen cases had neoplastic lesions in their duodenum (0.07%). Four of them were malignant lesions those included one duodenal carcinoma, one cancer of duodenal papilla, and two malignant lymphomas. All other nine neoplasms were adenomas. The first, the second, and the third portions of duodenum had one (7.7%), seven (53.8%), and five lesions (38.5%) respectively. A duodenal cancer located at the third portion of the duodenum. Ten cases were categorized as the superficial non-ampullary duodenal epithelial tumor (SNADET). Five of them (50%) located at the third portion of duodenum. The second and the first portions had four (40%) and one
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differences in 7 hormone levels: T, FSH, LH, E2, PRL, F, T4. Serum of girls from Pripyat

Results:

Radioimmunoassay was used to determine the blood serum hormones: testosterone (T), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P4), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH).

Results: In surveys of girls from Pripyat we established statistically significant differences in 7 hormone levels: T, FSH, LH, E2, PRL, F, T4. Serum of girls from Pripyat compared with serum of girls from Kyiv had levels of T, FSH, LH higher than in controls (p < 0.05). In Kyiv girls differences were detected in 3 of 11 hormone LH, T4, K. Common to the two groups was an increase in cortisol to 500nmol/L, and above. This was increase was larger in the girls from Kyiv. We can assume that prolonged activation of the pituitary-adrenal system in the inspected girls is the result of complex environmental and psychological factors, including damaging factors from the Chernobyl accident. Prolonged exposure to damaging factors can lead to suppression of basic adaptive system with the development of the primary functional adrenal insufficiency. Since this system in children has less spare capacity to adapt compared with that in adults it is easily exhausted and can lead to functional disorders in other endocrine axes - especially pituitary-gonads, and pituitary-thyroid gland.

Conclusions: Revealed abnormalities in the hormonal status of the girls surveyed, obviously, is the result of functional disorders of the endocrine system. Such dysfunction does not give explicit symptoms and thus remain unnoticed by the doctor. The girls identified with hormonal disorders, obviously, are a group at high risk for the occurrence of tumors caused by hormones.

Legal entity responsible for the study: Ukrainian-French medical center "Children of Chernobyl", NAS of Ukraine

Funding: Prominvestbank, bank "LIS"

Disclosure: All authors have declared no conflicts of interest.

The prevalence and characteristics of Barrett esophagus of general population in high risk area for esophagus cancer in North China (GXiAn County)

Background: The prevalence of Barrett Esophagus (BE) has progressively increased in recent years in western countries, and there is a trend of increasing incidence in China. The Xi’an County is a high risk area for esophagus cancer. It has been about 30 years since the Project of Early Detection and Treatment for cancer was initiated there. The data of cancer registration had been included by Cancer Incidence in Five Continents (International Agency for Research on Cancer, IARC). However, no epidemiological data of BE has been reported.

Methods: From 2013 to 2014, residents officially registered by CXian’s authority aged between 40 and 69, were mobilized to participate in the screening project. The process followed the protocol of the Project of Early Detection and Management. All eligible individuals took endoscopy. If any abnormal lesion was found, biopsies were taken for pathological examination. The diagnosis criteria were according to AGA criteria 2008. Demographic data and endoscopic characteristics were retrospectively analyzed.

Results: Of 24,081 eligible residents, 5548 participated in the screening. The compliance rate was 23.54%. Of the 5548, 2319 were male, the other 3229 were female, giving a sex ratio of 0.72. The mean age was 53.57 ± 7.95. The mean BMI was 25.30 ± 3.41. 4481 accepted endoscopy, of which 2484 biopsies were taken for further pathological examination. The rate of biopsy was 58.89%. 226 met the endoscopic diagnosis criteria of BE (4.63%), of which 118 were island types (52.21%), 75 were tongue types (33.19%), 33 were circumferential types (14.60%). In those endoscopic BE, only four long segment BE (1.77%), the others were short segment (98.23%). 28 BE were pathologically confirmed. The detection rate of BE was 0.50%. Of those confirmed cases, 16 were male, the others female, the sex ratio was 1.33. The mean age was 56.36 ± 8.08, and the mean BMI was 24.87 ± 3.33. 15 had family history of cancer (53.57%). Only 5 had typical reflux symptoms (17.86%), 4 of which were diagnosed GERD according to AGA (14.28%).

Conclusions: Barrett esophagus is an important precancerous lesion in the high-risk area of North China. It’s necessary for it to be brought into the Project of Early Detection and Management as a routine item.

Legal entity responsible for the study: China-Japan Friendship Hospital

Funding: Ministry of Science and Technology of People’s Republic of China.

Disclosure: All authors have declared no conflicts of interest.

The hormonal status of girls from Kyiv and evacuees from Pripyat

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Background: A study was conducted to determine hormone levels among girls from Pripyat and Kyiv 5 years after the Chernobyl accident. Variations of hormonal status in pre- and pubertal girls evacuated from the town Pripyat and girls from the city of Kyiv were revealed.

Methods: We investigated the hormones in the blood serum of 749 girls from Pripyat (50%) and Kyiv (245). Age girl was 10-15 years. The study was conducted in Kyiv with the support of Ukrainian-French medical center "Children of Chernobyl".

Radioimmunoassay was used to determine the blood serum hormones: testosterone (T), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), cortisol (F), triiodothyronine (T3) thyroxine (T4), progesterone (P4), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH).

Results: In surveys of girls from Pripyat we established statistically significant differences in 7 hormone levels: T, FSH, LH, E2, PRL, F, T4. Serum of girls from Pripyat compared with serum of girls from Kyiv had levels of T, FSH, LH higher than in controls (p < 0.05). In Kyiv girls differences were detected in 3 of 11 hormone LH, T4, K. Common to the two groups was an increase in cortisol to 500nmol/L, and above. This was increase was larger in the girls from Kyiv. We can assume that prolonged activation of the pituitary-adrenal system in the inspected girls is the result of complex environmental and psychological factors, including damaging factors from the Chernobyl accident. Prolonged exposure to damaging factors can lead to suppression of basic adaptive system with the development of the primary functional adrenal insufficiency. Since this system in children has less spare capacity to adapt compared with that in adults it is easily exhausted and can lead to functional disorders in other endocrine axes - especially pituitary-gonads, and pituitary-thyroid gland.

Conclusions: Revealed abnormalities in the hormonal status of the girls surveyed, obviously, is the result of functional disorders of the endocrine system. Such dysfunction does not give explicit symptoms and thus remain unnoticed by the doctor. The girls identified with hormonal disorders, obviously, are a group at high risk for the occurrence of tumors caused by hormones.

Legal entity responsible for the study: Ukrainian-French medical center "Children of Chernobyl", NAS of Ukraine

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Disclosure: All authors have declared no conflicts of interest.

What is the optimal annual interpretive volume for a radiologist reading screening mammograms?

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Background: A positive association between the annual screening volume and the performance of screening radiologists has been suggested. The majority of studies show that there is little or no relation between radiologist’s interpretive volume and sensitivity, but the association of interpretive volume to false-positive rate, cancer detection rate, recall rate or interval cancer rate is still unclear. As a consequence, many countries have adopted very different maximum reading volume requirements (e.g., from 500 to 5,000 per year). The aim of the study is to evaluate whether an optimal annual interpretive volume for screening radiologists can be established.

Methods: A systematic review to assess the evidence of the association between radiologist interpretive volume and breast cancer screening performance outcomes, following standard Cochrane Collaboration guidelines and methods, was carried out. The following databases were searched until November 2015: The Cochrane Database of Systematic Review, DARE, MEDLINE, EMBASE, PIQ, and McMaster Health Systems Evidence. GRADE methodology was applied.

Results: From an initial set of 872 unique citations, 14 studies (2,935 radiologists, 32 screening services) were included. These studies retrospectively analysed information from prospective databases, except one study with a cross-sectional design. The evidence suggested an association between a higher annual screening volume and a lower false-positive rate, with an optimal performance around 1,500 to 4,000 readings per year (moderate quality evidence). Cancer detection rate appeared to be optimised at about 1,000 readings per year in the context of high volume facilities (moderate quality evidence). Recall rate appeared to increase above 3,000 readings per year (low quality evidence). The effect on false-negative rate and interval cancer rate is unclear (very low quality evidence).

Conclusions: Screening radiologists should perform at least 1,500 to 4,000 screening mammograms per year to keep the performance outcomes at an acceptable level. This recommendation is provisional (due to uncertainty about the association between caseloads and the net benefits of screening), and conditional (depending on the availability of radiologist meeting the requirements).

Legal entity responsible for the study: European Commission, Joint Research Centre

Funding: European Commission, Joint Research Centre

Disclosure: All authors have declared no conflicts of interest.

A novel way to visualise tumour related angiogenesis and detect breast tumours in women: A combined clinical and optical method for breast cancer screening of well-women in Ghana

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Background: Late stage neoplastic breast lesions abound in Ghana, especially, late-stage early-age breast cancer and therefore low survival rates after treatment of breast cancer is prevalent. The median age at diagnosis for breast cancer is 39 years hence screening mammography ("the gold standard") is not suitable and also not...
readily available in Ghana. Preliminary data suggests transillumination offers a new mode of early detection for neoplastic breast lesions and is not limited by age.

**Methods:** In all, over 10,000 women who were manually screened for breast lesions during mobile breast screening clinics with the view to enhance early detection were offered transillumination with the breastlight/breast-i (optical tomography used to detect angiogenesis) as well. These optical devices, (the breastlight/breast-i) developed by David J. Watmough were used to visually observe angiogenesis around breast tumours and lesions. The breastlight/breast-i operates on the principles of light travelling through tissues and the specific wavelength of light absorption by Haemoglobin in blood.

**Results:** Here we report on a total of 9,962 “well women”, initially using Breastlight but since 2014 using a new improved instrument Breast-i. The significance of a dark shadow arises because light is multiply scattered within the breast tissues and excess absorption of red light occurs at a wavelength of around 620nm when a cancer is present, caused by angiogenesis. A sensitivity of 94.4% was obtained for detecting breast cancer.

**Conclusions:** The advantage of Breast-i is that there is no radiation exposure, no tissue compression and it is quick and easy to carry out the examination. This is probably the largest study of its kind in the world.

**Legal entity responsible for the study:** Mammocare Ghana, Highland Innovation Centre and University of Cape Coast, Ghana.

**Funding:** Highland Innovation Centre.

**Disclosure:** All authors have declared no conflicts of interest.

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**1336P**

**Multigene panel testing for breast cancer patients at high risk for hereditary cancer**

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**Background:** Next-generation sequencing and identification of additional cancer susceptible genes has made it feasible for patients at risk test for various hereditary cancer syndromes. We have evaluated the performance of a customized multi-gene panel test and hereditary cancer risk assessment in high-risk patients.

**Methods:** A total of 252 patients with multiple primary cancers or high-risk hereditary cancer were identified. Among them, 179 patients (71.0%) had multiple primary cancers, 27 patients (10.7%) were diagnosed bilateral breast cancer younger than 40 years, breast cancer patients with family history, and 2% in very young (<25 years old) breast cancer patients. Mutations annotated in dbSNP, clinVAR and Ensembl comparative genomic resources were analyzed and reviewed.

**Results:** In the 65-gene panel test, pathogenic or likely-pathogenic mutations (PM) were identified in 78 (31.0%) patients. Frequency of all PM or likely-PM was 59%, 40%, and 9% in bilateral breast cancer with ≤40 years, breast cancer patients with ≥2 family history, multiple primary cancer, and breast cancer patients <25 years, respectively. The distribution of high-risk genes for hereditary cancer including CDH1, MLH1, MSH2, MSH6, MUTYH, PTF1, TP53, BRCA1, and BRCA2 were 55% in multiple primary cancer patients, 35% in bilateral breast cancer with ≤40 years, 18% in breast cancer patients with ≥2 family history, and 2% in very young (<25 years old) breast cancer patients, respectively.

**Conclusions:** Using a 65-multigene panel test we have identified PMs, especially associated with hereditary cancer. We can use these results for detecting high-risk group of hereditary cancer in breast cancer patients.

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**1338P**

**Evaluation of breast cancer patients with genetic risk: Before and after a multidisciplinary heredofamilial cancer unit implementation**

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**Background:** Identifying Breast Cancer (BC) patients with genetic risk reduces the mortality for BC and the prevention of second tumors. In 2010, we implemented a multidisciplinary Heredofamilial Cancer Unit (HFCU). We hypothesized that the creation of this HFCU improved the referral and proper preventive management of patients with BC and genetic risk.

**Methods:** We retrospectively compared family history record (FHR), referral of patients with high-risk to genetic counseling (GC), detection and management of BRCA1/2 mutation (+) patients, of BC patients diagnosed and treated in our institution before (July 2007-June 2010, first period) and after the HFCU creation (July 2010-June 2013, second period). Main characteristics of 541 patients were also analyzed.

**Results:** 893 patients from the first period and 902 in the second met inclusion criteria. Mean age at diagnosis was similar in both groups (57.6 ± 57.8 ± p NS). 142 patients (15.9%) vs 70 (7.8%) were not analyzable because a lack of complete information to establish the genetic risk (p < 0.05). Among evaluable patients, 194 (23.8%) vs 225 (27%) had one or more risk criteria (p NS). FHR, referral rate and preventive surgeries (2 bilateral mastectomy (BM) and 1 bilateral salpingo-oophorectomy (BSO) in the first period vs 12 BSO and 9 BM in the second) in BRCA+ patients increased in the second period (table). 56 risk patients diagnosed in the first period with risk criteria were referred to the HFCU, detecting 9 additional BRCA2 mutations. 84.6% of BRCA1+ patients and 91.7% of BRCA2+ were diagnosed ≤50 years. 76.9% of BRCA1+ patients and 100% of BRCA2+ had one or more first-degree relatives with breast cancer. 69.2% of BRCA1+ patients had triple-negative BC (TNBC), whereas 83.3% of BRCA2+ patients had luminal BC.

**Conclusions:** There is a clear improvement in FHR, referral and preventive surgeries in BC patients with genetic risk after the implementation of the HFCU. TNBC predominates in BRCA1+ while luminal in BRCA2+.

**Legal entity responsible for the study:** Hospital General Universitario Gregorio Maranon

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**Disclosure:** All authors have declared no conflicts of interest.
All authors have declared no conflicts of interest.

Breast cancer in young women survivors of pediatric cancer

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Background: Patients cured of a pediatric cancer have shown increased risk of secondary tumors. Women long-term survivors have a significantly increased risk of developing breast cancer (BC) at a young age. Screening programs for early detection of BC are well-established in healthy women. On the contrary, there is a scarcity of guidelines for young women cured of a pediatric cancer. We try to develop a multidisciplinary screening outcome.

Methods: Patients were identified from Pediatric Oncology Department at the University Hospital La Fe. The cohort consists of young women with a prior diagnosis of a pediatric tumor, if treatment had included chest RT and/or high dose of alkylating chemotherapy before bone marrow transplantation. Patient data were extracted for each patient according to age. If any suspicious lesion was detected, the patient was transferred to the Breast Unit in Oncology.

Results: 17 women (10 Hodgkin Lymphoma, 4 Non Hodgkin Lymphoma and 3 Ewing Sarcoma) were contacted. 4 women refused to be included (2 due to psychological reasons, 1 pregnancy, 1 just-diagnosed with BC). Median age was 27 years and median time since end-of-treatment was 14.5 years. The initial treatment was chemotherapy (CT) alone in 14 patients (64.2%) and combination CT and radiotherapy (RT) in 7 (35.8%). 7 cases were irradiated (5 Hodgkin Lymphoma, 1 Non Hodgkin Lymphoma, 1 Ewing). The median dose of irradiial RT was 22.6 Gy (range 15-25.2 Gy). Breast exams were normal. MRI exams were performed in 8 of 13 patients. It revealed a suspicious lesion in 1 patient (BI-RADS 4) and benign lesions in 3 patients (BI-RADS 2). MRI studies of the remaining 4 patients were normal, without findings. Benign lesions were fibrofatty. The patient with the malignant lesion was an invasive ductal carcinoma with positive hormonal receptors and negative Her-2 neu (1 case).

Conclusions: We have developed a complete early-detection BC program for our survivors at risk.

Legal entity responsible for the study: Hospital Universitario y Politècnico La Fe

Funding: GVA grant

Disclosure: All authors have declared no conflicts of interest.

Leveraging six sigma instruments to optimize cancer screening in an urban community hospital

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Background: In 2010, the U.S. Department of Health and Human Services implemented a quality improvement initiative known as “Healthy People 2020” designed to improve outcomes across a broad array of illnesses by 2020. Within the category of cancer, the initiative’s goals include improving screening rates. As poor socioeconomic status has long been associated with lower screening and higher mortality rates, and given the low socioeconomic status of much of our patient population, our institution has implemented Six Sigma techniques designed to decrease variability in cancer screening measures, reduce healthcare disparities, and improve screening outcomes.

Methods: Beginning in the 4th quarter of 2013, our hospital’s Ambulatory Care department implemented a bimonthly rapid cycle evaluation of physicians designed to analyze a variety of patient care metrics including breast and colorectal cancer screening rates in each physician in our panel. Data for each quarter was systematically distributed to each physician and a care navigation team was assembled to ensure screening compliance via patient outreach in the form of phone calls and certified mail.

Results: Data from the 1st quarter of 2014 until the 2nd quarter of 2015 were collected from two sites affiliated with our institution’s outpatient service. During that timeframe, the rate of colorectal screening—which includes colonoscopy and serial fecal occult blood testing—increased at Site 1 from 79.1% to 84.4% and at Site 2 from 70.8% and 75.3%. With respect to breast cancer screening, the rate at Site 1 remained virtually unchanged (90.4% and 90.1%) while the rate at Site 2 increased from 80.7% to 86.3%.

Conclusions: As our intervention has demonstrated, cancer screening may be optimized by the use of a low-cost, easily implementable, and easily replicable intervention leveraging Six Sigma instruments. In light of the challenges affecting our institution’s predominately African-American and Latino populations—particularly as they relate to access to care and timely cancer diagnoses—our intervention may go a long way toward reducing disparities and improving outcomes in these increasingly disadvantaged populations.

Proposal of a stage-specific surveillance strategy for colorectal cancer

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Background: Current guidelines from ESMO, ASCO, NCCN, and JSCCR recommend intensive postoperative surveillance for colorectal cancer following curative resection, using periodic CEA test, CT scanning, clinic visit, and colonoscopy. However, the optimal frequency of these standard modalities and the duration of surveillance remain debatable.

Methods: We analyzed cohort data from 22 member institutions of the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer. Patients who underwent curative surgery for stage I to IV colorectal cancer between 1997 and 2006 were included. We assessed the cumulative incidence of recurrence, and estimated the proportion of patients in whom recurrences were detected by the standard surveillance modalities every year after surgery (death rate, DR).

Results: A total of 18,841 consecutive patients were identified. Overall recurrence rates in stage I, II, III, and IV were 4.2%, 14%, 32%, and 75%, respectively. Surgical resection of recurrence in each stage was performed in 55%, 51%, 43%, and 42% of patients, respectively. More than 95% of recurrences in every stage were first suspected or detected by the standard surveillance modalities. Over 80% of recurrences occurred within the first 5 years in stage II and 3 years in stage IV, 5 years in stage I. Among patients with a 5-year recurrence-free survival, 2.2% in stage III and 7.0% in stage IV still experienced recurrence after the 5-year postoperative period. The DR in stage I was consistently low during the surveillance period. The DR in year 1 to 3 of stage II was about twice that of stage I. Furthermore, the DR of stage III was about twice that of stage II. In year 1 to 2 of stage IV, the DR was more than triple that of stage III.
Conclusions: These results suggest that a stage-specific approach to postoperative surveillance may improve the efficiency of detecting recurrences. Further study is needed for a prognostic non-inferiority assessment of this strategy.

Legal entity responsible for the study: Japanese Study Group for Postoperative Follow-up of Colorectal Cancer

Funding: Japanese Study Group for Postoperative Follow-up of Colorectal Cancer

Disclosure: All authors have declared no conflicts of interest.

1343P
Aspirin utilization, compliance and prevention of colorectal cancer – A single centre perspective

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Background: Recent randomised controlled trials indicate daily low dose aspirin may reduce the risk of colorectal cancer by up to 20%. Aspirin is currently prescribed or self-administered regularly to prevent heart disease. Considering wider population-based chemoprevention against colorectal cancer, a greater understanding of community use, compliance, adverse effects, and patient awareness is required. We performed a prospective observational study on aspirin use in our local population to examine these issues.

Methods: A prospective data collected using questionnaires over a six month period from every patient attending surgical clinic at our hospital.

Results: Aspirin: 137 patients; male: 72, female: 65. Mean age 65.8 years (range: 23-100). 76.6% were taking aspirin 81mg. 32.9% did not know what dose they were taking. 5.8% were taking a dose over 300mg. 62% of patients were taking aspirin on physician advice. 25.6% of patients stated they never missed a dose of aspirin, 39% admitted to missing doses, 3% never took it. 5.8% reported side effects. Only 9.5% were aware of the anticancer effects of aspirin. Non-aspirin: 135, female: 248. Mean age 53.8 (18-80). 1% used aspirin in the past and ceased treatment. 4.7% knew of anticancer effects. Mean ages differed significantly (unpaired t-test, p < 0.001). Patients not on aspirin were more likely to be female, younger, with heart disease / diabetes or on more than 5 medications (Fisher’s exact test, p = 0.0005, p < 0.0001, p = 0.0002). No significant differences between groups in anticoagulation use, additional NSAID use or smoking (p = 0.51, p = 0.20, p = 0.19).

Knowledge of anticancer effect showed trend to significance (p = 0.06) favoring the aspirin group, with main sources of information being the media or internet.

Conclusions: Patients on aspirin in our community are older, with less co-morbidities and concurrent medication use. Overall awareness of anticancer effect was suboptimal, physician involvement in this area is low. Over 40% of our patients are non-compliant with treatment. These results have implications for any potential use of aspirin for chemoprevention of colorectal cancer.

Legal entity responsible for the study: Gurpreet Singh Ranger

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

1344P
Knowledge of cervical cancer preventive strategies among market women in Nigeria

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Background: Cervical cancer is the fourth most common cancer worldwide for females and the seventh most common cancer overall. Nigeria, a developing country, ranks tenth globally and fifth in Africa, has a mortality rate of 22.9 deaths per 100,000 with 14,000 new cases being diagnosed annually. In an effort to reduce this mortality rate, this research was undertaken to assess the level of awareness, attitude and practice of common cervical cancer preventive strategies such as screening and the treatment of precancerous lesions using LEEP as a case study among women.

Methods: A descriptive design using simple random sampling methods with self-administered questionnaires or interview methods (for illiterate) were used to collect data from the sample population. Market women were used (4 major markets in Ibadan) because they provided a sample population of women both in their reproductive and menopausal groups, with various level of literacy. Data was analyzed using the SPSS version 15.

Results: Of the total 100 respondents, only 55% had heard about cervical cancer while just 35% had heard about cervical screening test. 26% cited schools while 16% of the 35% cited mass media as their sources of awareness about the disease. 96% agreed that women should be aware about the procedure, 85% agreed that it could reduce maternal mortality rates from cervical cancer.

Conclusions: Despite limitations in funding, it is suggested that more research work can be done to assess possible ethical beliefs towards contraceptives, HPV vaccine and sexual practices and how they affect cervical cancer incidence and mortality rates.

Legal entity responsible for the study: Adetule Cecilia Yemisi

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

1345P
Prevalence of cyp1b1 mutations among lung cancer patients

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Background: Lung cancer is the leading cause of cancer death in the world. The most important risk factor is smoking. Only about 10% of patients never smoked, on the other hand, only about 15% of smokers get lung cancer. One of the possible reason can be individual, genetic factors. This is supported by the evidence of more frequent occurrence of this disease in first-degree relatives of patients with lung cancer. In addition, there are many reports about lung cancer relationships with certain genetic disorders.

Methods: Correlation of CYP1B1 gene polymorphisms (variants C142G, G355T and C4326G) with the risk of lung cancer was analyzed. The selection of these genes is associated with their impact on the transformation of carcinogens contained for instance in tobacco smoke (CYP1B1). The frequency of CYP1B1 polymorphisms between 112 patients with lung cancer and the control group, consisting of 100 neonatal umbilical cord blood, is compared. Patients were also evaluated in terms of gender, type of cancer, the amount of pack-years and age of onset. Association of genetic variations with lung cancer were analyzed in terms of single nucleotide polymorphisms, haplotypes and combination of genotypes.

Results: Statistically significant higher incidence of G allele variants of C142G polymorphism and allele C of C4326G polymorphism in patients with lung cancer was found. G355T polymorphism showed no statistically significant differences in terms of allele frequencies between the compared groups. Haplotypes GTC and haplotypes GT (C142G-C355T) and GC (C142G-C4326G) occur significantly more frequently in the lung cancer group. Genotype combinations containing allele G of polymorphic variants C142G occur significantly more often in patients with lung cancer.

Conclusions: The results demonstrate a significant relationship of some polymorphisms with the risk of developing lung cancer. Inclusion of genetic data into screening could contribute to more accurately determine the population at risk of lung cancer and improve the results of lung cancer screening.

Legal entity responsible for the study: Wojewodzki Szpital Zespolony im. L. Rydygiera w Toruniu 2. NZOZ Pracownia Genetyki Nowotworów w Toruniu

Funding: 1. Wojewodzki Szpital Zespolony im. L. Rydygiera w Toruniu 2. NZOZ. Pracownia Genetyki Nowotworów w Toruniu

Disclosure: All authors have declared no conflicts of interest.

1346P
Naturally occurring immune response against biologically and clinically relevant targets

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Background: Few studies evaluate the immunogenicity of biological relevant targets in tumors with high-world prevalence and early relapse such as ovarian, triple negative breast cancer (TNBC), multiple myeloma (MM), etc. Some tumor targets are immunogenic but are not relevant for tumor survival such as CEA, CA-125, CA-19-9, etc. and have failed in vaccines clinical trials. Only a few studies focus on the biological and clinical relevance of tumor antigens such as MUC1, Her-2, etc. Aberrant up-regulation of some proteins that are involved in cancer relapse has shown to be a mechanism by which some auto-proteins become immunogenic and potentially targets of both humoral and cellular adaptive immune response. We evaluated whether putative relevant proteins that are found in high incidence of several cancers and associated with poor prognosis could be recognized by the humoral immune response.

We further investigate if the humoral immune response against these proteins may predict relapse and overall survival.

Methods: Four broad-spectrum proteins known to be overexpressed in several tumors and associated with early relapse were identified by systematic reviews. Indirect peptide
ELISA was used to evaluate humoral immune response using all predicted peptides from these proteins. 50 stage IV cancer patients and 50 age-matched controls were studied. We identified those MHC-I and MHC-II peptides using computer-based algorithms from Ape-1, Fascin, RCAS1 and VCP.

Results: Fascin and VCP peptide mixes are immunogenic in all cancer-interrogated patients and in some controls. Antibody responses were significantly elevated in cancer patient’s sera when compared to controls (Ape-1 p = ns, Fascin p = 0.0016, RCAS1 p = ns and VCP p < 0.0013). Patients with an average OD > 0.38 against at least 2 peptides for 2 proteins had better overall survival (p = 0.005).

Conclusions: Discussion: All tumors studied reacted by peptide indirect ELISA at least against 2 peptides of overexpressed proteins involved in important biologic pathways and this is the first approach to design a broad spectrum multi-peptide vaccine to prevent relapse. Humoral immune response may also predict the clinical outcomes in malignancies that tend to relapse in short period of time.

Legal entity responsible for the study: Centro de Investigación de Cáncer en Sonora

Funding: Centro de Investigación de Cáncer en Sonora

Disclosure: All authors have declared no conflicts of interest.

### Table: 1348P

<table>
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### Conclusions:
It is concluded that the incidence of malignancy is increasing in alarming way in the last 25 years. It is mainly due to the effect of environmental Pollution (i.e. Air, Water and Earth Pollution ) from the previous Wars in Iraq. This increasing incidence of cancer is associated with a younger age group especially with regard to Breast and GIT malignancies; however, high percentage of those malignant patients got good benefit by treatment with chemotherapy and or Hormonal therapy in Babylon Oncology Center and R.T. in Baghdad Radiotherapy Center.

Legal entity responsible for the study: Babylon Health Directorate

Funding: Sharif Abood

Disclosure: All authors have declared no conflicts of interest.
Unsung heroes of lung cancer: Perspectives from caregivers in the lung cancer Canada survey

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Background: Lung cancer (LC) is a major cause of cancer death, morbidity and loss of function. Caregivers (CGs) of patients (pts) with LC provide emotional, physical, and financial support, but their contribution is under-reported. The Lung Cancer Canada Survey aimed to study the impact of LC diagnosis and treatment on pts and CGs.

Methods: This online survey for pts and CG was conducted in August 2015. The questionnaire covered demographics, emotional issues and stigma, symptom burden, quality of life, treatment experiences, and unmet needs. Anonymously collected results were collated by Lung Cancer Canada.

Results: 91 pts and 72 CG completed 163 interviews. Most CGs were partners (54%) or parents (38%). 60% were the primary CG, and 79% were former CGs: 68% of their care receivers had died. Most CGs coped well (79%), but stressors included care-receiver’s declining health, their own emotional and financing responsibilities, fatigue, depression, and respiratory complaints were the most challenging symptoms for CGs and pts. CGs reported more negative feelings than pts: anxious/stressed 61%/42%, depressed/hopeless 32%/11%, and cared for 17%/38%, encouraged 11%/25%. CGs felt less support than pts from their healthcare team (75%/92%) and family/friends (65%/87%). Treatment satisfaction was lower among CGs: only 58% felt very/somewhat satisfied (v 82% of pts). 68% of CGs reported a negative stigma attached to LC, 35% felt there was less empathy toward LC than other cancers, and 38% felt they had to advocate harder for LC than other cancers. Notably, some CGs (8%) and pts (5%) reported a lack of compassion from medical professionals after a LC diagnosis. 50% of CGs reported a negative household financial impact: 69% reduced working hours, and 48% quit their jobs. More empathy, support services and financial resources were suggested to help alleviate CG burden.

Conclusions: This is the most detailed report on the experience of CGs of pts with LC, and highlights their reactions to the illness, and the associated prejudice and stigma. It also led to opportunities for Lung Cancer Canada to decrease CG burden through support initiatives such as CG-specific educational materials and the inclusion of CGs through peer-to-peer support programs.

Legal entity responsible for the study: Lung Cancer Canada

Funding: Lung Cancer Canada

Disclosure: P. Wheateley-Price: Advisory Boards for Merck, Lilly, Boehringer Ingelheim and AstraZeneca. All other authors have declared no conflicts of interest.

Psychosocial quality of life in 30 survivors of bilateral retinoblastoma

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Background: Retinoblastoma (Rb) is the most common intraocular tumor in childhood. Approximately one-third of the cases are bilaterally affected. The cure rates have improved but the data on psychosocial quality of life are limited.

Methods: We analyzed the psychosocial domain quality of life (QOL) in 30 survivors of bilateral Rb using PedsQLTM 4.0 generic core scale in local language, which has been validated in the Indian population. The self-reported questionnaire was filled in by children of more than 5 years of age who had completed treatment for more than 12 months. The psychosocial aspect is represented by social, emotional and school domains of QOL. The QOL was compared with 25 siblings using student’s t-test. Factors predicting QOL were assessed.

Results: The median age of Rb survivors was 86 (range, 61-190) months and male: female ratio was 3:1. The median age at diagnosis was 12 (range, 1-16) months. 83% (25/30) underwent enucleation of the worst eye, whereas both eyes could be preserved in 5 patients. All the patients received VEC (Vincristine, Etoposide and Carboplatin)-based chemotherapy and the median number of chemotherapy cycles was 6 (range, 6-12). Radiotherapy was given in 83/30 (26%) patients. The psychosocial QOL was significantly worse in Rb survivors compared with controls. The emotional health domains of QOL (fear, anger and sleeping) were significantly lower in Rb survivors. Difficulties in maintaining friendships and competing were reported in the social health domain. In school health domain, there was significantly higher absenteeism due to sickness and hospital visits among Rb survivors. Age, sex, IRSS stage and previous radiotherapy did not affect the psychosocial QOL.

Table: 1351P Comparison of psychosocial QOL of survivors of bilateral retinoblastoma and their siblings

<table>
<thead>
<tr>
<th>Health Domain</th>
<th>RB Survivors (n = 30)</th>
<th>Healthy Siblings (n = 25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
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<td>Social</td>
<td>74.7 ± 10.1</td>
<td>83.9 ± 6.6</td>
<td>0.0003</td>
</tr>
<tr>
<td>Emotional</td>
<td>76.3 ± 9.6</td>
<td>82.9 ± 7.8</td>
<td>0.01</td>
</tr>
<tr>
<td>School</td>
<td>70.2 ± 11.2</td>
<td>84.4 ± 4.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>77.1 ± 8.2</td>
<td>83.5 ± 5.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions: We found a significantly worse psychosocial QOL in bilateral Rb survivors, including the school, emotional and social aspects. However, no predicting factors for poor QOL were found.

Legal entity responsible for the study: N/A

Disclosure: All authors have declared no conflicts of interest.
Empowerment in adolescents and young adults (AYA) with cancer and its association with health-related quality of life

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Background: Cancer challenges the abilities of AYA cancer patients to achieve developmental milestones such as completing education, getting an intimate relationship, pursuing gainful employment or having children. Problems concerning self-esteem, autonomy, body image, fertility and sexuality may have a negative impact on health-related quality of life (HRQoL) of AYA cancer patients. A construct that may be associated with HRQoL is empowerment, defined in the cancer setting as feeling of being able to manage the challenges of the cancer experience and having a sense of control over one’s life. The aims of this study were to assess the levels and associated factors of empowerment among AYA cancer patients and its relationship with HRQoL.

Methods: Patients 18-35 years old at time of cancer diagnosis and visiting the AYA clinic of Radboud university medical center Nijmegen were invited to fill in questionnaires about empowerment, potential associated factors (autonomy-connectedness, coping, social support and psychological distress) and HRQoL. (physical, psychological, social, religious functioning and total QoL). T-tests and linear regression analyses were performed.

Results: Eighty-five AYA patients completed the questionnaire (response 29%). The mean age at diagnosis was 27.5 years (SD = 4.6). A third of the AYA patients were high empowered. Moderate empowered AYA patients were more often female, had lower levels of autonomy, received less social support meeting their needs, had more coping problems and higher levels of psychological distress compared to their high empowered counterparts (all p < 0.05). Regression analyses showed that psychological empowerment was independently associated with physical (Beta = 0.35), psychological (Beta = 0.50), social (Beta = 0.40) and religious functioning (Beta = 0.32) and total HRQoL (Beta = 0.52; all p < 0.01).

Conclusion: Empowerment is an important factor related to HRQoL. Intrapersonal (autonomy, coping) and interpersonal (social support) factors were strongly associated with empowerment and therefore may serve as components for developing age specific empowerment interventions among AYA cancer patients to improve HRQoL.

Legal entity responsible for the study: N/A

Funding: Radboudumc

Disclosure: All authors have declared no conflicts of interest.

Professional reintegration after cancer treatment: factors influencing return to work

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Background: The majority of patients treated for cancer face the complex challenge of reintegrating themselves professionally, during or after cancer treatment. There is an obvious need for interventions that facilitates professional reintegration. This study is a quantitative analysis of factors associated with probability to return to work, as a basis for guidelines for interventions in this respect.

Methods: A multicenter questionnaire study was initiated in two cancer centers enabling the recruitment of 104 patients (NOLV Aalst = 39, NGZA Antwerp = 65, sex: male = 12, female = 92, M Age = 48.41). Professionally active patients were selected between 18 and 58 years of age, 8-10 months after cancer diagnosis with curative purpose and without signs of relapse. Through binary logistic regression the predictive value of work attitude, the experienced support from colleagues and supervisors, self-efficacy, perceived positive and negative social interactions, fatigue, anxiety and depression on whether or not to work 8 to 10 months after diagnosis were examined. Statistical analyses were made with SPSS 21.

Results: From the results the imported model shows a significant predictive value (y2 (12) = 64.56, p < 0.001) for working or not. Patients still in treatment, have a less positive work attitude, were tired, had less anxiety or reporting more positive social interactions, were less likely to be working (p = 0.03, p = 0.06, p = 0.18, p = 0.08, p = 0.09).

Conclusion: The observation that more positive social interactions are perceived negatively related to return to work, seems counterintuitive, but might be related to a high level of protection by social interactions. In addition, the higher level of anxiety in working patients may be related to experiencing difficulties in returning to work and the associated tensions in a working environment, which entailed by the resumption of multiple social roles. While future research is needed to further clarify these relationships, the results suggest that interventions for return to work best take into account both physical and psychosocial factors. The results also contributed to the development of a hospital-wide health care program in cooperation with government authorities for employment.

Legal entity responsible for the study: Dr. Nathalie Adam

Funding: Stichting tegen Kanker

Disclosure: All authors have declared no conflicts of interest.

Cancer occurrence and cure: the power of the mind

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Background: Making sense of illness, and cancer in particular, is a long-standing quest. In addition to scientific explanations (cancerogenesis), a layperson’s outlook on the natural history of the disease is a complex mix of “how?” and “why?” Psychological factors have been extensively surveyed as a potential cause for cancer in different cultural backgrounds.

Methods: In 2014, we conducted two surveys in France among laypersons with no history of cancer (N = 1463, age range 40-75) and physicians (N = 301, age range 27-70). Interviews were conducted between June 12 and July 10, 2014 (lay persons) and between July 9 and August 8, 2014 (physicians). Questions focused on the perceived causes of cancer and the way to achieve cure.

Results: Among the general population of our survey, 7% of women declared that psychological stress is one of the five main causative factors for breast cancer in an international survey among students in 2000, this rate was 1.7% for Koreans, 20.4% for Bulgarians and 8.3% for French women. In 2014, this factor was reported by 3% of female physicians in France (Significant difference with laypersons P = 0.04). In terms of cure, 89% of laypersons (France, 2014) quoted “state of mind” as a powerful tool and 73% of physicians (P < 0.01). Interestingly, laywomen who mentioned psychological status as a causative factor for breast cancer are also more likely to see it as a curative tool (P < 0.01).

Conclusions: It therefore appears that in 2014, psychological factors are considered more as a tool to help cure cancer than as a risk to be controlled. Laypersons saw psychological factors as playing a far more important role in both the origin and the cure of cancer than physicians did. There is also a statistical correlation between these two viewpoints.

Legal entity responsible for the study: Edifice surveys were funded by Roche S.A.

Funding: Edifice surveys were funded by Roche S.A.

Disclosures: F. Eisinger, X. Pivot, L. Grellier, J-Y. Blay, S. Couraud, A-B. Cortot, J-F. Morère: Honorarium fees from Roche. C. Lhomel: Employee of Roche. All other authors have declared no conflicts of interest.
Stoicism and its relation with clinical-pathological variables in patients with resected cancer undergoing adjuvant chemotherapy treatment


Background: The objective of this study is to analyze the relationship between stoicism, gender, age, location and stage of the tumor, and compare the scores with two international samples.

Methods: A multicentre, prospective, observational study that uses a website to gather clinical data and questionnaires that are given before and after adjuvant chemotherapy for patients with non-metastatic resected cancer. The Liverpool Stoicism Scale (LSS) was applied to assess stoicism and Student’s t-test was used to analyze the correlation according to gender, age, location and stage of the cancer.

Results: A total of 243 patients were recruited in 11 centers. Mean age of the patients was 59 years, and 58% were male. The most frequent tumors were colon (41%), breast (35%), and stomach (10.8%), in stage III (38.5%). The significantly higher Stoicism scores were obtained in: men (p < .001), over 55 years old (p < .001), patients with non-metastatic disease (p = 0.02) and vitality (56.7 ± 13.6 vs. 50.1 ± 8.7, p = 0.03) reported by younger patients. It can be hypothesized that they are worried by the problems that will occur after discharge.

Conclusions: The elderly are more sensitive to physical pain and exhibit a reduced vitality after surgery than younger patients. It can be hypothesized that they are worried by the problems that will occur after discharge.

Legal entity responsible for the study: University of Padua

Funding: University of Padua

Disclosure: All authors have declared no conflicts of interest.

Abstracts

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Therapeutic and Quality of Life in Patients with Non-metastatic Resected Cancer


Background: In recent years, there has been a growing interest in evaluating the relationship between spiritual wellbeing and health in cancer patients. Our goal is to analyse the trustworthiness and validity of the spiritual wellbeing scale (FACIT-Sp), and the link between the three factors of the scale and the Quality of Life (QoL) in a sample of cancer patients.

Methods: NEO-KOPING® is a prospective, multi-centre study. A total of 297 patients from 13 centers were checked and 195 were finally admitted, 33 were rejected because they did not match the inclusion criteria and 69 were excluded because they had not completed all the protocol at the time of the analysis. All the patients had a non-metastatic resected cancer with intention to cure and were candidates to adjuvant chemotherapy. The variables included in this study were sociodemographic, clinical, pathological and psychosocial, and the questionnaires used were FACIT-Sp scales and EORTC-QLQ-C30.

Results: Mean age of the patients was 58.3 years (SD = 12.2), and 60% were women. The main cancers were: colon (41.5%) and breast (34.4%). The results show that FACIT-Sp gives an excellent internal consistency (α = 0.901). Statistically significant correlations were found between: the meaning of life and faith, meaning of life and peace, meaning of life and quality of life, meaning of life and faith, meaning of life and quality of life, meaning of life and peace, meaning of life and quality of life, meaning of life and peace, meaning of life and quality of life, meaning of life and peace, meaning of life and quality of life, meaning of life and peace, meaning of life and quality of life, meaning of life and peace, meaning of life and quality of life, meaning of life and peace, meaning of life and quality of life, meaning of life and peace, meaning of life and quality of life, meaning of life and peace, meaning of life and quality of life, meaning of life and peace, meaning of life and quality of life, meaning of life and peace.

Conclusions: FACIT-Sp is a trustworthy and reliable tool to evaluate spiritual wellbeing in cancer patients with non-metastatic resected cancer, and it is a useful and interesting concept for future investigations in oncology.

Legal entity responsible for the study: Sociedad Española de Oncología Médica

Funding: Sociedad Española de Oncología Médica

Disclosure: All authors have declared no conflicts of interest.
Evaluation of burnout syndrome and personalized intervention in the medical oncology unit of the Second University of Naples (SUN)

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Background: Burnout and stress occur frequently among oncology healthcare workers. These syndromes affect quality of life with detrimental effect on personal wellness and patient-physician relationship. The objective of our research was to estimate the levels of stress and burnout among the healthcare workers of the oncology department of SUN and to evaluate the possible effects on personal and professional life in order to organize an useful therapeutic approach.

Methods: Burnout and stress levels were measured among 35 oncology healthcare workers (9 physicians, 19 residents, 6 nurses) at our institution. Burnout levels were assessed by using the "Link Burnout Questionnaires" (LBQ), consisting of 24 items, scored with Likert scale (0 – 6). Stress levels were analysed by using the "Health Professions Stress and Coping Scale" (HPSCS), a self-report questionnaire. We calculated three severity levels (low, medium and high) for burnout (0-8, 9-24, 25-36) and stress (<1260, 1260-1540, >1540), according to the score intervals obtained in each section.

Results: Questionnaires were administered in March 2016. Median age of our population was 30 years (25 - 65) and 77% were females. Total burnout level was scored as medium in the overall population, with no major differences among physicians, residents and nurses. Total stress level was found medium-high in the overall population with no difference among the three groups. Stress and burnout levels were correlated with age, sex, years of service and working hours in the overall population and among the three professional groups: in LBQ test, IP level (Professional Ineffectiveness) was more prevalent among residents (p < 0.03), in the same group a trend toward a significant correlation was found between DR (Relationship Deterioration) and working hours (p = 0.09).

Conclusions: These results represent a basic evaluation of stress and burnout prevalence in our institution. No major differences were found among the subpopulations analyzed. A psychoncologist intervention centered on an individual rather than a group approach has been adopted. Tests will be repeated after three months. Further data will be presented at that time.

 Legal entity responsible for the study: Department of Internal and Experimental Medicine "F. Magrassi", Second University of Naples

Funding: Department of Internal and Experimental Medicine "F. Magrassi", Second University of Naples

Disclosure: All authors have declared no conflicts of interest.

Evaluation of burnout, anxiety and depression in physicians of an oncology hospital

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Background: It is increasingly apparent that physicians present high levels of burnout, symptoms of anxiety and depression. They have worked to the limit of their possibilities. However, it is important to plan subsequent interventions to improve their quality of life, increase their job satisfaction and assure that they see themselves as important and productive at work.

Methods: A cross-sectional study including holders physicians and residents physicians. For data collection we used socioeconomic, demographic and health-related questionnaires; variables characterization questionnaires related to physicians daily life, Maslach Burnout Inventory; and the hospital anxiety and depression scale (HADS). Data collection method was with Survey Monkey. For screening criteria, the following were considered: anxiety (HADS-A ≥ 11), depression (HADS-D ≥ 11), emotional exhaustion (EE ≥ 27), depersonalization (DP ≥ 10) and personal fulfillment (PF ≤ 52), which were correlated to physicians’ socioeconomic, demographic and occupational characteristics. All variables with p < 0.2 in the univariate logistic regression analysis were included in multivariate logistic regression model (backward stepwise regression). The statistical significance criterion was 5%.

Results: Of the 323 emails sent via Survey Monkey, 237 (73.3%) physicians responded, of which 4 (1.2%) refused to participate. The evaluation was 227 (70.2%) physicians, corresponding those who completed all survey items. Of those, 143 (63%) were male, aged 21–40 years (44%), 140 (61.7%) are married, 92 (40.5%) worked in the institution corresponding those who completed all survey items. Of those, 143 (63%) were male, 67% had a stable relationship, 51% had kids and 18% were still under his training in oncology. Median age was 37.5 years, and median time spent in oncology practice was 10 years. Among them, 61 (57.6%) consume alcoholic beverages regularly, and 10 (9.5%) were considered addicted according to the CAGE questionnaire. According to Ramirez et al and Grunfeld et al criteria. BS was found in 70 (65.4%) and 8 (7.5%) of physicians. According to Ramirez et al criteria, female gender (p = 0.038), not having children (p = 0.022), were related to the risk of having BS. On multiple analyses, however, none of these characteristics impacted on the prevalence of BS. According to Grunfeld et al criteria, female gender (p = 0.010), not having children (p = 0.038), training physician (p = 0.041), more than 40 working hours per week (p = 0.056) not having time for physical activities (p < 0.001) and fast visit duration (p = 0.033). None of these characteristics were associated to BS in MV analysis.

Table: 1360P Uni- and multiple analysis for factors associated to Burnout Syndrome; UV: univariate analysis; MV: multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Ramirez et al.</th>
<th>Grunfeld et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>N (%)</td>
<td>P</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>12.5</td>
</tr>
<tr>
<td>Children</td>
<td>No</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Oncology Training Status</td>
<td>Compelled</td>
<td>-</td>
</tr>
<tr>
<td>Under Training</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weekly work hours</td>
<td>≤ 40 h per week</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&gt; 40 h per week</td>
<td>-</td>
</tr>
<tr>
<td>Mean visit duration</td>
<td>≤ 20 min</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>≥ 20 min</td>
<td>-</td>
</tr>
<tr>
<td>Physical Activities</td>
<td>≤ 2 h per week</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 h per week</td>
<td>-</td>
</tr>
</tbody>
</table>

Conclusions: Burnout Syndrome is a condition highly frequent among Brazilian physicians. We could not identify relevant factors influencing its high prevalence in this setting.

Legal entity responsible for the study: Centro Oncologico Antonio Ermito de Morais, IRB

Funding: Personal funds from the authors

Disclosure: All authors have declared no conflicts of interest.
Effect of mindfulness training on quality of life and distress in early breast cancer patients treated with endocrine therapy

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Background: Endocrine therapy (ET) prescribed in breast cancer can cause side effects that mimic menopausal symptoms and can thereby affect patients’ quality of life. Mindfulness-Based Stress Reduction (MBSR) is a structured group intervention based on meditation and its application in daily life. It has been shown effective in improving quality of life (QoL) and reducing psychological distress in cancer patients but not specifically in patients receiving ET, which was the aim of this study.

Methods: Newly diagnosed breast cancer patients scheduled for (any) ET and/or radio- but no chemotherapy were recruited to participate in a standardized, 8-week MBSR program provided by a certified trainer (one 3h-session/ week). Clinical outcomes were general QoL and distress measured through the short World Health Organisation Quality of Life scale (WHOQOL-Bref) and the short revised Depression Anxiety Stress Scales (DASS-21-R) before the start, at the end, and 6 months after the end of MBSR.

Results: Twenty breast cancer patients, all receiving tamoxifen (11 had also radiotherapy), completed the study. Mean age was 57.5 ± 7.4 years. At the start of MBSR, 11 were postmenopausal, mean time since diagnosis was 157 ± 65 days and mean time on ET was 99 ± 68 days. As shown in Table 1, the WHOQOL-Bref total score did not improve after MBSR. In contrast, there was a significant decrease of the DASS-21-R total score, though only the comparison of scores before the start vs after 6 months reached significance (p = 0.023, two-tailed paired Wilcoxon tests; scores before vs after MBSR: p = 0.186).

Table: 1361P Mean scores for global QOL and psychological distress of patients treated with tamoxifen receiving MBSR

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Before start of MBSR</th>
<th>At end of MBSR</th>
<th>6-month after end of MBSR</th>
<th>P (Friedman ANOVA, two tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHOQOL-Bref total score</td>
<td>97.4(10)</td>
<td>96.4(8.3)</td>
<td>98.9(10.4)</td>
<td>0.170</td>
</tr>
<tr>
<td>DASS-21-R Total score</td>
<td>28(14.8)</td>
<td>22.5 (13.4)</td>
<td>19.5(17.4)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Conclusions: MBSR did not improve global QoL in breast cancer patients treated with tamoxifen. Given their rather high QoL, MBSR might not have been offered at an appropriate time. Still, MBSR was beneficial as it significantly lowered their psychological distress (up to at least 6 months).

Legal entity responsible for the study: Jeroen Mebis

Funding: VZW Think Pink

Disclosure: All authors have declared no conflicts of interest.
Background: Access to new, innovative, medicines potentially fulfilling unmet medical needs are of paramount importance to patients. European patients will on average have to wait 6 to 12 months as compared to their US counterparts to get access to new anti-cancer drug. Yet, 1 do not receive any direct fund for the development of new drugs, access to scientific advice (at reduced or fully waived fee) will be possible at the stage of 'proof of principle' (i.e. prior to Phase 1) whereas large Pharma can enter the stage at the stage of ‘proof of concept’ (i.e. around Phase 2).

Conclusions: The PRIME scheme was launched in spring 2016 and a number of projects were selected as appropriate for inclusion. Whether this process will lead to earlier access to new, innovative medicines for patients with clear unmet medical need is too early to say. At any rate, this process is the first attempt by EU regulators to optimise the use of the current medicines legislation to foster innovation and hopefully improve review time for medicines in areas with high unmet medical needs such as oncology.

Legal entity responsible for the study: N/A

Funding: NDA Advisory Services Ltd

Disclosure: S. Thirstrup: I work as a full-time employee for NDA Advisory Services Ltd, which is a global scientific and regulatory consultancy firm for the pharmaceutical industry. I do not receive any direct fund for my work from pharmaceutical developers and/or manufacturers.

Do contemporary randomized controlled trials meet ESMO thresholds for clinically meaningful benefit?

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Background: ESMO has developed a framework for evaluating the magnitude of clinical benefit (ESMO-MCBS) of new cancer therapies. We evaluate the extent to which contemporary randomized controlled trials (RCTs) are designed to detect differences in outcome that meet the proposed ESMO thresholds for clinically meaningful benefit (CMB).

Methods: All RCTs evaluating systemic therapy for breast, non-small cell (NSCLC), colorectal, and pancreatic cancer published 2011-2015 were reviewed. Two authors abstracted data regarding trial characteristics and applied the ESMO-MCBS to study results. Data from the statistical methods section were used to determine if the RCT was powered to detect an effect that would meet the threshold for CMB. Factors associated with being powered for small effect size included disease (79% lung, 71% GI, 61% breast, p = 0.038), treatment intent (82% palliative, 37% curative, p < 0.001), therapy (molecular 86%, cytotoxic/hormone 58%, p = 0.015), primary endpoint (OS 82%, survival surrogate 61%, p = 0.001), and funding (72% industry, 50% non-industry, p = 0.014). On adjusted analysis, only treatment intent remained significant. Among all 277 RCTs, the experimental therapy was statistically superior to the control arm in 143 trials; the results of 29% of these trials met the ESMO threshold for CMB. Factors associated with meeting the CMB threshold included disease (40% breast, 29% lung, 14% GI, p = 0.018), treatment intent (56% curative, 20% palliative, p < 0.001), and primary endpoint (37% survival surrogate, 24% OS, p = 0.013). On adjusted analysis only treatment intent and GI cancer remained significant.

Conclusions: Less than one-third of RCTs with statistically significant results meet ESMO thresholds for clinically meaningful benefit, and this represents only 15% of all published trials. Investigators and funding agencies should adopt more stringent thresholds for meaningful benefit in the design of future RCTs.

Legal entity responsible for the study: Queen’s University

Funding: Kingston General Hospital

Disclosure: All authors have declared no conflicts of interest.

Factors affecting job retention amongst cancer survivors five years after diagnosis: evidence from the French VICAN survey

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Background: Each year, 355,000 new individuals are diagnosed with cancer in France, nearly half of them are in working age (20 to 65 years). Only 35% of cancer survivors are employed at the time of diagnosis in 2010 whereas 78% of them had a professional activity five years later. The aim of the study was to identify factors associated with job retention amongst cancer survivors.

Methods: A French national survey on life conditions of cancers survivors diagnosed in 2010. Patient questionnaires were administered 2 and 5 years after diagnosis. The questionnaire dealt with access to healthcare, recovery after treatments and impact of the disease on personal and professional life in the two and five years following diagnosis, respectively (VICAN national surveys 2012 and 2015). Medical data were collected from a questionnaire completed by the physician who initiated cancer treatment, and information from the national medicoadministrative database on reimbursement data and hospital discharge records. A multinomial logistic regression was used to identify factors associated with job retention rather than switching or losing the job held before the diagnosis.

Results: Among the 1,139 cancer survivors aged 17-58 at diagnosis, 982 (86%) were employed at the time of diagnosis in 2010 whereas 78% of them had a professional activity five years later: 60% remained in the same job than five years ago and 18% have been in another occupation. The factors positively associated with the job retention during five years after a cancer diagnosis: educational level above high school graduation, open-ended job at the time of diagnosis, working in public sector and having had a working time reduction in the two years following cancer diagnosis. The factors negatively associated with job retention was radiotherapy, which negatively affect return to work.

Conclusions: National guidelines are needed to better take in consideration cancer survivors with no university degree and private employees in order to help them to return to work. Improving information on working conditions is necessary to get better understanding of the professional issues faced by individuals with cancer.

Legal entity responsible for the study: UMR 912 SESSTIM INSERM - RD - AMU

Funding: National Institut of Cancer (Institut National du Cancer, INCa)

Disclosure: All authors have declared no conflicts of interest.

Second cancer screening among 5-years women cancer survivors (French National Survey VICANS)

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1CIRS PACA, SESSTIM-INSERM UMR912- RD - AMU, Marseille, France. 2INSERM UMR912, SESSTIM-INSERM UMR912- RD- AMU, Marseille, France

Background: Cancer survivors have an increased risk (36%) to develop cancer compared to the non-cancer population. Improvement in cancer detection and treatment has led to an important increase of the number of long-term cancer survivors, many of them being at risk of second cancer. Face to the lack of information on cancer screening practices in this population, we decided to study such practices among women cancer survivors using the VICANS data. The national cancer screening recommendations exist for cervical cancer screening (Pap smear) (every 3 years between 25 and 65 years).
Methods: VICANS is the first national French survey on life conditions, prevention practices and medical follow-up of cancer survivors five years after diagnosis. Data has been collected from patient questionnaire, personal medical file and medical insurance databases. Patient questionnaire includes questions on new cancer screening before interview. Univariate and multivariate analyses have been performed to compare cancer women to French non-cancer women regarding their screening practices.

Results: VICANS surveyed 1149 women including 654 (60%) women with non-breast cancer and 1111 (88%) with non-cervical cancer. We found an underutilization of mammography screening in the non-breast cancer group compared with women in the general population (78% vs 87%). Concerning report of Pap smear in the past 3 years, no significantly differences were found between non-cervical cancer survivors and the general population (83% vs 81%). Use of a Pap smear test is strongly associated with having had a screening mammography. Several associated factors with tertiary prevention practices was found such as psychological state (anxiety level), physical characteristics (BMI) and life style (tobacco use).

Conclusions: Survivorship care plans are needed to improve information of survivors and to increase physicians awareness of the importance of tertiary prevention, especially among the cancer survivors who are at high risk to develop a second cancer.

Legal entity responsible for the study: French National Institute of Health and Medical Research (Inserm)

Funding: French National Institute for Cancer (INCA)

Disclosure: All authors have declared no conflicts of interest.
Results: First and second sets included 303 and 227 patients, respectively. Patients from the first and second sets differed in tumor site (urological (25.7% vs 15.4%) and gastrointestinal (17.8% vs 27.8%)) and in lung metastases incidence (9.9% vs 48.9%). Overall survival (OS) at three months was 87.8% (95%CI [83.5, 91.0], first set) and 91.2% (95%CI [86.7, 94.2], second set). Presence of a ‘life expectancy’ inclusion criterion did not improve the 3-month OS (HR 0.86, 95%CI [0.2, 1.7]; p = 0.2233).

Independent factors of early death were an ECOG score of 2 (OR 13.3, 95%CI [4.1, 43.4]), hyperfructoseuria (OR 5.5, 95%CI [1.9, 16.3]) and anemia (OR 2.8, 95%CI [1.1, 7.1]). Some predictive factors but with different association levels were found in the second set. Using the first set, ROC analysis shows a good discrimination to predict early death (AUC: 0.89 at 3 months and 0.86 at 6 months). In the overall population, patients with 0, 1, 2 and 3 risk factors had a rate of 3-month early-death of 2.4% (7/289), 13.7% (24/175), 37.7% (20/53) and 60% (6/10) and a rate of 6-month early-death of 6.5% (19/292), 28% (49/175), 47.2% (25/53) and 70% (7/10), respectively.

Conclusions: Risk modeling in two independent cancer populations based on 3 simple factors of early death may allow identifying patients who may not benefit from a phase II trial investigational drug and may, therefore, represent a helpful tool to select patients for phase II trial entry.

Legal entity responsible for the study: Institut Bergonié Comprehensive Cancer Center

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Disclosure: All authors have declared no conflicts of interest.

1374P Socioeconomic position and mortality among patients with prostate cancer: influence of mediating factors

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Background: Men with low socioeconomic position experience higher mortality after a prostate cancer diagnosis compared with men with higher socioeconomic position, however, the specific mediators of this association are unclear. We therefore evaluated the influence of potential mediators on the association between socioeconomic position, and prostate cancer specific and all-cause death in prostate cancer patients.

Methods: We conducted a cohort study of prostate cancer patients in the Danish Diet, Cancer and Health study. All patients completed questionnaires and anthropometric measurements at enrollment. Information on vital status, educational level, income, and comorbidity was obtained by linkage to Danish nationwide registries. Clinical data and anthropometric measures were collected from medical records at diagnosis. Cox proportional hazard models were used to compute hazards ratios for all-cause and prostate cancer specific death according to socioeconomic position and potential mediators.

Results: We included 953 prostate cancer patients identified among 27,179 male participants in the Diet, Cancer and Health study who were followed for a median of 6.5 years (interquartile range, 6.4-11.2 years). Patients with low education were more often overweight or obese at baseline. The likelihood of aggressive cancer was almost equally distributed between educational levels. Obesity at baseline, but not at diagnosis, was associated with increased prostate cancer specific and death of all causes. Low socioeconomic position was associated with increased prostate cancer specific and all-cause death. The increased mortality tended largely to be explained by tumor aggressiveness, comorbidity, treatment, and metabolic indicators, except for patients in the lowest income group.

Conclusions: Our study confirmed the prior assumption that socioeconomic position is associated with increased mortality after prostate cancer. The increased mortality could largely be explained by lifestyle and clinical parameters.

Legal entity responsible for the study: The study was approved by the regional ethical committees on human studies in Copenhagen and Aarhus (J nr.(KF11)-037/01) and by the Danish Data Protection Agency.

Funding: The present study is supported by the Danish Council for Independent Research – Medical Science [Grant No. 271-07-06B19], The Scientific Committees of the Danish Cancer Society [Grant No. 225 06 051] and The Health Insurance Foundation [Grant No. 2006B095].

Disclosure: All authors have declared no conflicts of interest.

1372P Risks and benefits of phase 1 oncology trials in the era of personalized medicine

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Background: Although crucial to developing new anti-cancer treatments, phase I trials in oncology can be considered as ethically controversial. Critics argue that they have no therapeutic intent and offer participants no reasonable prospect of benefit. However, early access to potentially effective new drugs especially targeted therapies can be an opportunity for patients.

Methods: We reviewed all non-pediatric phase 1 oncology trials published in English in 2014 and 2015. Characteristics of trials and patients were retrieved from the publications. We assessed the rates of serious adverse events and treatment-related deaths. Patients were divided into three groups: patients who were treated with a study drug, patients who were exposed to an experimental intervention but did not receive the drug, and patients who were included in the trial but not treated.

Results: We analyzed 236 trials involving 8267 participants, all of whom were assessed for toxicity and 7128 (87%) of whom were assessed for a response to therapy. 107 trials (45%) focused on a specific population (tumor type and/or molecular profile) and 59 trials (25%) were conducted in all comers.

Conclusions: Phase I trials provide a key opportunity for patients.

Legal entity responsible for the study: Institut Bergonié, Bordeaux Comprehensive Cancer Center

Funding: Institut Bergonié Comprehensive Cancer Center

Disclosure: All authors have declared no conflicts of interest.

1372P Causes of death among cancer patients as a function of calendar year, age, and time after diagnosis

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Background: Our objectives are to characterize the causes of death among cancer patients as a function of: (i) calendar year, (ii) patient age, and (iii) time after diagnosis. We will analyze data from two sets of patients: (1) the patients who died of cancer and non-cancer death, (2) identify those who might profit from intensive screening for second cancers, and (3) identify cancers that would most benefit from further research.

Methods: We used death certificate data in SEER Stat 8.2.1 to categorize cancer patient death as being due to index-cancer, non-index-cancer, and non-cancer cause, in the USA from 1973 to 2012. In addition, data were characterized with standardized mortality ratios (SMRs), which provide the relative risk of death as compared to all persons in the USA. A total of 28 cancers and 13 non-cancer causes of death were analyzed. A minimum of 1,000 person-years-at-risk were necessary for analysis of each disease site.

Results: With respect to objective I, there were 1,895,788 deaths. 1,065,324 died due to index-cancer, 204,453 died due to non-index-cancer, and 626,011 not due to cancer. Over the entire time period, the greatest relative decrease in index-cancer death (generally from > 60% to < 30%) was among those with cancers of the testis, kidney, bladder, endometrium, breast, cervix, prostate, ovary, anus, colorectum, melanoma, and lymphoma. Index-cancer deaths (typically > 40%) were stable among patients with cancers of the liver, pancreas, esophagus, and lung, and brain. Non-cancer causes of death were highest in patients with cancers of the colorectum, bladder, kidney, endometrium, breast, prostate, testis; >40% of deaths were from heart disease. For objectives II/III, the cancers with high SMRs tended to be of immunologic/hematologic origin, and lung cancer. The highest SMRs were from non-bacterial infections, particularly among < 50 year olds (e.g. SMR >1,000, p <0.001) with leukemias/lymphomas; SMRs were inversely associated with patient age at time of diagnosis. The big SMRs of the non-cancer causes were < 50 SMR (p <0.001) during follow-up of > 2-10 years, prostate cancer patients had increasing SMRs from Alzheimer’s disease, as did testicular patients from suicide.

Conclusions: The risk of death from index- and non-index-cancers varies widely among primary sites. Risk of non-cancer deaths varies as the proportion of cancer deaths, particularly for young patients in the year after diagnosis.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
Conclusions: A novel, effective and efficient pathway for patients who might otherwise be diagnosed as part of EP. This pilot shows the feasibility of a nurse-led service based in an oncology department, and a high level of user satisfaction. This model of acute diagnostic oncology clinic should be considered as an addition to existing outpatient cancer diagnostic pathways.

Legal entity responsible for the study: Chelsea & Westminster Hospital NHS Trust

Funding: Cancer Research UK Macmillan NHS England

Disclosure: All authors have declared no conflicts of interest.

Profile of cancer patients who visit a specialized emergency room in São Paulo, Brazil

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Background: Instituto do Câncer do Estado de São Paulo (ICESP) is a Brazilian university hospital dedicated to cancer treatment. Since there are about 19,000 outpatient appointments, 4,300 chemotherapy sessions and 5,400 radiotherapy sessions monthly, a focused emergency room (ER) has been created, so as to assist our patients. This study describes the main reasons that lead patients to ER, in order to improve medical assistance.

Methods: We performed a descriptive and retrospective cohort study, using medical records of all patients attended at the ER from 01/24/16 to 02/07/16, excluding ones referred from the day hospital unit. A two-way ANOVA (α = 0.05) was followed by a Fischer’s LSD test to assess the prevalence of different cancer sites between regular appointments and ER visits.

Results: In the period, 990 patients totaled 933 visits to the ER. The most frequent affections were pain (86.4%), fever (10.3%), muscle weakness (7.2%), dyspepsia (6.5%), bleeding (4.5%) and swelling (4.0%). Most common ER patients cancer sites were colorectal (14.4%), breast (33.4%), head & neck (19.0%), hematological (19.0%), esophageal/ stomach (8.8%), lungs (7.2%), prostate (6.5%), urinai tract (6.0%) and liver/ bile ducts/ pancreas (5.7%), uterus (3.3%) and skin (2.9%). From 05/08/2016 to 08/2013, the most frequent diagnoses in ICESP were: prostate (14.8%), colorectal (12.5%), breast (12.1%), head & neck (9.2%), skin (8.4%), esophageal/ stomach (7.9%), lungs (6.5%) and hematological (6.0%). The most common cancer types treated in ICESP are also the ones most often seen in ER patients, but for prostate (p = 0.0008) and skin cancers (p = 0.0460), significantly less common in the ER than in regular appointments. Surprisingly, colorectal and breast cancer were the most frequent among patients in our ER, while most of them were under chemotherapy and so, visited the outpatient unity frequently during the same period. Initial tests did not establish a link between complaints and tumor site.

Conclusions: Our study shows the most frequent complaints of cancer patients who visit our specialized ER and demand intervention for treatment or diagnosis. A deep analysis of final ER diagnoses is required, so that multidisciplinary, educative and preventive actions should be taken, in order to avoid visits to the ER.
More than 50% consider ASCO and ESMO website/newsletters useful. The more useful sections of ESMO “OncologyPro” are considered the “Guidelines and Practice” (66%) and the “Oncology news” (49%). Nearly 50% have participated in ESMO fellowships/educational activities and 50% are planning to participate in some of these. 39% of oncologists are satisfied with ESMO fellowships and 83% are satisfied with ESMO educational activities. 55% use LinkedIn, 42% ResearchGate, 18% Facebook and 7% Twitter, while 15% have their own Personal website. For search engine 28% use GoogleScholar, 14% PubFacts and 15% Google. Lack of time and financial issues are considered as the main problems for continuous professional development while clinical practice and on-line medical resources are considered the most effective ways to achieve continuous medical education.

Conclusions: The majority of oncologists are well informed about the educational opportunities in their countries and in Europe. An increasing number of oncologists get familiar and satisfied with the new technologies in the Web-Era and use them for continuous oncology education and career development.


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1926P Elicitation of public preferences for lung cancer screening using three screening modalities

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Background: Since early detection of lung cancer can substantially increase overall survival, there is increasing attention for lung cancer screening. This study aims to identify public preferences for lung cancer screening and to identify subgroups with distinct preferences.

Methods: The study was designed as a multi attribute elicitation experiment using swing weighting. Attributes were selected using interviews with three clinicians and a panel session with eight representative respondents. Included attributes were sensitivity, specificity, radiation load, duration of screening procedure, time until results, mode of screening (CT scan, breath or blood test) and location of screening (GP or hospital). A hierarchical clustering method was used to identify subgroups in the preference weights.

Results: In total, 1034 respondents from a representative Dutch panel aged between 40 and 80 completed the questionnaire. Respondent’s preferred breath analysis (45%) to blood samples (31%) or the CT-scanner (24%). 59% would prefer to be screened at their GP instead of the hospital. The three most important attributes were location of screening (0.18, SD = 0.16), mode of screening (0.17, SD = 0.14), and sensitivity (0.16, SD = 0.13). There was a distinction between preferences of subgroups focusing on organization of the screening service and preferences of subgroups focusing on clinical benefits of screening. Respondents with a lower education were more likely to belong to subgroups found organization of the services most important, while respondents with a higher education were more likely to find clinical benefit important (P < 0.01). There were no significant between-cluster differences with regard to gender, age, smoke status, sex or perceived risk.

Conclusions: Our results indicate that there is great potential for new screening technologies that can be used at a primary care facility, and that a one-size-fits-all approach for lung cancer screening is unlikely to provide the best value for the screening population.

Legal entity responsible for the study: Maarten Ijzerman

Funding: University of Twente

Disclosure: All authors have declared no conflicts of interest.

1361P Current or former smokers: Who wants to be screened?

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Background: Lung cancer screening (LCS) with annual low-dose CT scans reduced specific and overall mortality in a selected population (age 55-74 yrs, current or former [quit < 15 yrs ago] smokers > 30 pack-years). Participation is key to successful screening programs. We assessed smokers’ intention to take part in a hypothetical LCS program for smokers.

Methods: The EDIFICE French nationwide observational surveys assess behavior related to cancer screening programs. EDIFICE 4 was conducted from June 12 to July 10 2014 by phone interviews of a representative sample of 1602 subjects (age 40-75 yrs) using the quota method. To identify explanatory factors associated with the intention to take part in a LCS program, we performed 2 comprehensive multivariate stepwise logistic regression analyses: (i) in current and (ii) in former cigarette smokers (who quit < 15 yrs ago).

Results: Among those with no personal history of cancer (N = 1463), 263 current and 170 former cigarette smokers were analyzed in the 2 regression models. 36.4% and 26.3% respectively, intended taking part in a LCS program. In current cigarette smokers, the following were explanatory factors of the intention to take part: having been already screened for lung cancer (OR = 2.81, 95% CI [1.37-5.81]; P < 0.01), smokers < 30 pack-years (OR = 2.69 [1.21-6.30], P = 0.02), intention to stop smoking (OR = 1.96 [1.04-3.75], P = 0.04), low EPICE score (no precarity) (OR = 2.15; 95% CI [1.16-4.08], P = 0.02). In contrast, women (OR = 0.28; 95% CI [0.15-0.52], P = 0.01) were less inclined to undergo screening. Participation in other cancer screening programs, the Fagerström score, use of e-cigarettes, previous attempts to quit, and eligibility for screening were not significantly explanatory factors. Among former cigarette smokers, those with no comorbidities were less inclined to participate...
Toxoplasmosis: an overlooked infection in cancer patients

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Background: Toxoplasmosis is a widespread disease caused by the Apicomplexan, coccidian protozoan Toxoplasma gondii (T. gondii). Human prevalence rates for toxoplasmosis vary greatly in different parts of the world ranging from 0% in North America to 94% in Costa Rica and Guatemala. Once the host acquires the infection by ingestion, T. gondii crosses the intestinal epithelium, disseminates into the deep tissues and traverses biological barriers to reach sites where it causes severe pathology. Normally, the immune response efficiently prevents the dissemination of the parasite. In immunocompromised hosts, however, such reactivation may be more frequent, leading to a massive and potentially fatal recrudescence.

Methods: Blood samples were collected from 150 immunocompromised patients having different types of malignancies as well as 50 immunocompetent individuals as a control group, to assess the seroprevalence of anti-T.gondii antibodies. The “CTK biotech Onctis Tons IgG IgM Rapid Test Cassette” was used according to the manufacturer’s enclosed manual for the detection of infection.

Results: In our study, 34 cases of toxoplasmosis were detected. Toxoplasmosis was higher in patients’ group than in control group. Among cancer patients, prevalence of T.gondii was significantly higher (20% & 4% for IgG and IgM respectively) compared with control (8% and 2%) (p = 0.003). Toxoplasmosis was higher in patients having solid organ tumors (24%) than in patients with hematological malignancies (12%) (p = 0.06). On the other hand, the type of treatment doesn’t seem to affect the prevalence of T.gondii. The prevalence in patients treated with chemotherapy was equal to the prevalence in those treated with irradiation (28% both).

Conclusions: T. gondii is an opportunistic parasite that remains a serious cause of morbidity and mortality in immunocompromised patients. However, screening for this parasite is usually omitted in non-HIV immunocompromised persons such as patients having malignancy. Proper diagnosis and treatment of these patients before starting treatment is mandatory as it can save their lives.

Legal entity responsible for the study: Faculty of Medicine, Cairo University

Disclosure: All authors have declared no conflicts of interest.
Methods: A retrospective cohort study was conducted of breast cancer patients who had been treated at North West Cancer Centre from the period of 2008 to 2015. Demographic variables were summarised and estimates of Kaplan-Meier survival for the cohort and breast cancer subtypes were generated. Cox models were used to investigate time to breast cancer-related death for cancer stage, grade, age and distance from the treatment centre. Hazards of death associated with time from diagnosis until treatment and surgery were also assessed.

Results: The cohort comprised of 285 patients that were treated at North West Cancer Centre. Mean and median age was 60 years (range 35-95), three were males. One hundred and twenty-six (44%) patients had screen-detected breast cancer. One hundred and fifty-two (53%) patients had breast cancer surgery, and 117 (41%) underwent mastectomy. Intrinsic histotype subtypes Luminal A, Luminal B HER2 positive, Luminal B HER2 negative, HER2 over-expression and triple negative (basal-like) were 75 (29%), 37 (14%), 98 (37%), 12 (4.6%) and 41 (16%) respectively. One hundred and fifty-six (55%) patients received adjuvant chemotherapy, 189 (66%) patients have been on adjuvant endocrine therapy and 149 (52%) patients had adjuvant radiotherapy. Five-year observed survival was 86.9% (95% CI 80.7 – 91.3). Adjusted analysis showed that increasing time from diagnosis until treatment and surgery were associated with a greater hazard of death (P < 0.001). There was insufficient evidence to suggest increasing time from diagnosis until surgery and treatment were associated with hazard of death.

Conclusions: Survival outcome of breast cancer at our regional centre is relatively comparable to Australia wide breast cancer survival. Increasing age and breast cancer stage were associated with a greater hazard of death in adjusted analyses.

Legal entity responsible for the study: Hunter New England Human Research Ethics Committee.

Funding: North West Cancer Centre, Tamworth, NSW 2340 Australia.

Disclosure: All authors have declared no conflicts of interest.

**1386P**

**BREAST CANCER FAST TRACK PROGRAMME - EVOLUTION AND GUIDELINES TO PRIORITISE PATIENT REFERRAL**

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**Background:** In our country there are a breast cancer (BC) Screening (45-70) but actually some patients are diagnosed out of it so Breast cancer fast-track program (BCFP) has proved to be an effective system to efficiently assess symptomatic women to prompt diagnose. The aim of the study is to develop a clinical prediction rule in order to better identify BC to reduce time interval between patient referral by the primary care (PC) physician to the specialist, diagnosis of BC, and start treatment.

**Methods:** From 2009 to 2015 we analyzed retrospectively all proposals sent from PC to the specialist, diagnosis of BC, and start treatment. From 2009 to 2015 we analyzed retrospectively all proposals sent from PC with suspected BC to the oncology coordinator at the Clínico-Malvarrosa Health Department in Valencia. We studied the different variables for which patients were referred to BC to evaluate which variables could be related to an increased chance of developing BC. Variables recorded include the presence/absence of lump, inflammation, pain, ulceration, skin change, nipple changes and secretion of the nipple, mobility and family history. To investigate a grade of association we performed a Pearson Chi Square test using STATA program.

**Results:** 810 patients were considered for the study. 156 were diagnosed with BC (19, 3%). The mean age of 65, 6 years (27 – 94). 55 patients were between 45 and 70 years and 101 were over 70 years old. 55 patients were under 40 years old. 48% of the patients were under 50 years old. One hundred and sixty-eight (16.8%) patients were diagnosed with localized stage. Above the patients diagnosed with BC, mean of time till specialist assessment was 16.8 days (Standard Deviation, SD 10.9); 11.5 days (SD 13.7) were needed for histopathological diagnosis, and first treatment was administered after 26.5 days (SD 18.2). Among the evaluated variables four were identified to be highly associated with BC: fixed chest lesion [Odds ratio, OR 12.7: IC 95% 7.8-20.7], lump lesion in women older than 50 years [OR 8.9: IC 95% 6.1-13.2], > 3 cm breast nodule [OR 8.2: IC 95% 5.3-12.8] and nipple secretion and retraction [OR 2.1: IC 95% 1.3-3.1].

**Conclusions:** The results show that the implementation of BCPF has managed to increase cooperation between the different healthcare professionals involved in BC leading to a faster diagnosis of BC. We have identified four variables that are significantly associated with BC, aiming to decrease the evaluation time by the leading to a faster diagnosis of BC. We have identified four variables that are significantly associated with BC, aiming to decrease the evaluation time by the

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**1388P**

**COMPETENCIES OF PHYSICIANS IN MANAGEMENT AND LEADERSHIP FOR A BETTER PALLIATIVE CARE TREATMENT**

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**Background:** • Assess current level of leadership and managerial competencies of public health professionals in our country, and; • Evaluation of the level of competence required (desired) governance and management of public health professionals in our country. The current level of competence refers to the knowledge, skills and leadership skills and managerial control of public health professionals.

**Methods:** This international scientific study was conducted in three phases: • Exhaustive review of scientific literature, • Panel consensus (consensus development panel), • Delphi study type (Delphi survey). First, a transversal (cross-sectional) study was undertaken to enable pre-testing (pilot) of the instrument of international standardized assessment of competencies of leadership and management in a practical sample of public health professionals in Tirana.

**Results:** The average age in the group of male (N = 62) public health professionals nationwide in this sample was 44.9 ± 10.6 years, while in women (N = 105) the average age of public health professionals was 44 ± 9.9 years. The average value of the output aggregate full-scale instrument consisting of 52 questions was lower for the current level of power management compared to the level necessary (desired) powers in leading public health professionals involved in this study nationwide in our country (138.4 ± 11.2 vs. 159.7 ± 25.3, respectively; P = 0.001, the difference was statistically meaningful [significant]). Gender matched comparisons with the current level of competence of management of public health professionals. Thus, the average value of aggregate output current leading women was higher than men (143.2 ± 13.5, 2), a result that was statistically negligible (P < 0.001).

**Conclusions:** This study was based on the application of a standardized instrument of contemporary design by experts and professionals and the best and recommended for a wide application in all countries of the European region. The application of the instrument in a nationwide representative sample in our country showed that the current level of managerial competence is lower compared with the level necessary (desired) for leadership competencies of public health professionals. The difference between the actual and the level of competence needed was statistically very significant. Even in our country, special importance should be given to education and vocational training based on competence, with a main focus towards the results of the work of health professionals and not simply knowledge acquired, which are necessary preconditions but not at all sufficient to cope with complex problems and to solve them.
effectively and efficiently. For this reason, education and competency-based training should definitely be included in all programs of continuing professional development in our country. Results of the current study will enable comparability studies.

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Disclosure: All authors have declared no conflicts of interest.

1390P
Changins trends in HIV and cancer
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Background: New anti-retroviral therapies have changed the natural history of HIV. Oncological disease increases its role against infectious complications. Currently, they are one of the main reasons for death and hospitalization. AIDS-defining cancers (ADCs) are Kaposi’s sarcoma, non-Hodgkin lymphoma (NHL) and cervical carcinoma. The other cancers, AIDS defining (NADCs).

Methods: An observational, retrospective study of a cohort of patients (p) with HIV–controlled in an Infectious Diseases unit and / or Medical Oncology for 11 years (2004 - 2014) was conducted. ADCs and NADCs are included, prognostic variables and epidemiological data were analyzed in relation to HIV and tumoral pathology.

Results: Of 780 p HIV, 101 tumors were diagnosed in 91 p (12%). Males 71%. Mean age 46 years. In order of frequency: NHL 21 p (23%), lung cancer 13 p (14%), Kaposi’s sarcoma 9 p (10%), hepatocellular carcinoma 7p (9%). The second malignancy was targeted in 10 p (11%). Since 2009 diagnosis of NADCs, it has increased 54 p (65%) opposite to ADCs 37 p (40%) (p = 0.027). 30 p (33%) have completed the response of the oncological pathology: 9p (11%) progression and 52 p (56%) death. 42 (46.2%) had viral load undetectable tumor diagnosis and 30p (33%) CD4 count > 500 / mm³. Of the 91 p, 48 p (53%) had HCV coinfection, 9p (10%) EBV or HPV and 50 p (54%) HBsAg positive. 57 p (63%) smokers 20 cigarettes / day, 26 p (29%) habitual consumption alcohol. 40 p (44%) had diagnosed > 10 years with HIV and 20 p (22%) HIV diagnosis was made simultaneously to the tumor. 5G from HIV diagnosis to tumor in ADCs was 2 years (CI 1.6-6.597) and NADCs was 14 years (CI 12.7 - 15.3) (p = 0.007). The 0.397 HR CI (0.204 to 0.773).

Conclusions: Our study confirms the appearance of malignancies earlier than in the general population and a significant increase in males not present in other studies. In relation to previous studies, we targeted the change of trend in the complications of p-HIV. NADCs prevalence is progressively higher than the ADCs. In our series, it was observed a reduction risk of death 60.3% for the patients with HIV infection and NADCs against the ADCs. It has also increased the prevalence of secondary tumors.

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Disclosure: All authors have declared no conflicts of interest.

1391P
Oral health disparities among privileged and underprivileged tribes of South India - a study on precancerous oral lesions prevalence
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Background: The tribal populations throughout India have remained socially and culturally alienated from mainstream Indian society until developmental and conservation activities in tribal areas forced interactions between them. Precancerous oral lesion is a major public health problem among South Indian tribes in Kerala state. The aim of this study was to explore oral health disparities among the underprivileged Paniya and the privileged Kurichya tribes of Wayanad, South India from the Precancerous oral lesions perspective.

Methods: A cross sectional survey was done among 600 Kurichya and 400 Paniya tribal populations of Wayanad District, India from January 2013 to June 2013 after approval from the Institutional ethical committee. A pretested structured questionnaire was used to collect data regarding study variables. Oral health survey form was used to record the oromusial status of the study population after obtaining informed consent.

Results: In this study Precancerous oral lesions was found to be far more prevalent among the underprivileged Paniyas than among the privileged Kurichyas (P < 0.001). The prevalence of Leskaplakia was found to be 42% amongst the Paniyas. This was much higher than the 2% found among the Kurichyas. Among the Paniyas a statistically significant relationship was observed between Precancerous oral lesions and poor access to oral health care (P < 0.001).

Conclusions: Determining possible interactions between geographical factors, distribution of risk factors, and prevalent cancers should guide preventive tasks against this important public health problem. According to our results western and southern parts of Turkey have the largest preventable numbers of tobacco and obesity related cancers.

Legal entity responsible for the study: N/A
Funding: N/A
Disclosure: All authors have declared no conflicts of interest.
Background: In the last decade there has been a significant improvement in response rates, progression-free survival and overall survival in metastatic colorectal cancer, as a result of the development of new standard chemotherapy combinations and appearance of target-specific drugs, such as bevacizumab. Given the high cost of this therapy and since the resources available for health care are increasingly limited, this study aimed to carry out a cost-effectiveness analysis of XELOX protocol plus bevacizumab in first line treatment for patients with metastatic colorectal cancer from the perspective of a public hospital focused on care and education.

Methods: The economic assessment employed a simple decision associated with Markov model, where costs are expressed in local currency (R$) and outcomes in months of life gained (MVG). This model used the TreeAge Pro 2013® software. It has crafted a model of Markov state transition in time horizon of 60 months, each model cycle corresponded to three months. The cost data were collected retrospectively by micro-costing, and obtained through the internal electronic data system of Clinical Oncology Division.

Results: The data effectiveness and the transition probabilities between the states health were calculated using data from clinical studies selected by systematic review. The difference improvement in months of life gained was 2.25 for an extra cost of R$ 47,833.57, which resulted in an increased cost-effectiveness ratio of R$ 21,231.43 per month gain life. In the sensitivity analysis, the variable that had the greatest impact was the effectiveness for clinical support health in XELOX. When this parameter was inserted in the model with the minimum value, the cost-effectiveness ratio increased R$ 7,814.47 and based on the maximum value that was for R$-29,614.12, meaning that the XELOX + Bev has become dominated by XELOX.

Conclusions: Considering the World Health Organization cost-effectiveness threshold (three times the value of GDP per capita), the XELOX + bev protocol it was not considered cost-effective. This study indicates a switch towards targeted therapies accounting for more than 80% of the melanoma treatments in 2015. Two particular classes of therapies, small molecules targeting the MAPK signaling pathway and immune-oncology agents replace conventional CTs. Besides MEK&BRAF inhibitors that already showed significant market shares in 2013, particularly antibodies against CTLA-4 or the PD-1/PD-L1 pathway are more commonly used in the TX of melanoma PTs. However, a population of 6% is still not tested for BRAF mutations. Therefore, further research is necessary to understand a missing uptake of novel TX options in the clinical practice.

Legal entity responsible for the study: IMS Health GmbH & Co. Ohg

Funding: IMS Health GmbH & Co. Ohg

Disclosure: All authors have declared no conflicts of interest.

Table: 1394P TX landscape of stage III/IV melanoma PTs *PTs included in a clinical trial or don’t receiving a systemic therapy were not considered

<table>
<thead>
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<th>TX regimens</th>
<th>2011</th>
<th>2013</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base (number of sample PTs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All PTs</td>
<td>244</td>
<td>346</td>
<td>587</td>
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<tr>
<td>CT</td>
<td>68.4%</td>
<td>43.3%</td>
<td>9.0%</td>
</tr>
<tr>
<td>PD1/PD-L1</td>
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<td>-</td>
<td>31.9%</td>
</tr>
<tr>
<td>MEK&amp;BRAF</td>
<td>5.3%</td>
<td>37.9%</td>
<td>44.8%</td>
</tr>
<tr>
<td>BRAF</td>
<td>10.7%</td>
<td>10.1%</td>
<td>31.9%</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>15.6%</td>
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</tr>
<tr>
<td>Others</td>
<td>87.6%</td>
<td></td>
<td>94.2%</td>
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</tbody>
</table>

Conclusions: This study indicates a switch towards targeted therapies accounting for more than 80% of the melanoma treatments in 2015. Two particular classes of therapies, small molecules targeting the MAPK signaling pathway and immune-oncology agents replace conventional CTs. Besides MEK&BRAF inhibitors that already showed significant market shares in 2013, particularly antibodies against CTLA-4 or the PD-1/PD-L1 pathway are more commonly used in the TX of melanoma PTs. However, a population of 6% is still not tested for BRAF mutations. Therefore, further research is necessary to understand a missing uptake of novel TX options in the clinical practice.

Legal entity responsible for the study: IMS Health GmbH & Co. Ohg

Funding: IMS Health GmbH & Co. Ohg

Disclosure: All authors have declared no conflicts of interest.
sarcoma

Randomized phase 3, multicenter, open-label study comparing evoestofamidine (Evo) in combination with doxorubicin (D) vs. D alone in patients (pts) with advanced soft tissue sarcoma (STS): Study TH-CR-406/SARC021


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Background: Evo is a hypoxia-activated prodrug preferentially activated under hypoxic conditions to release the DNA alkylator Br-IPM. A phase 2 study of Evo (300 mg/m²) with D (75 mg/m²) resulted in a 6 month progression free rate of 58%. A Phase 3 study, with pretreated advanced soft tissue sarcoma (STS) pts and pts with advanced soft tissue sarcoma, compared Evo + D vs. D alone in patients (pts) with advanced soft tissue sarcoma (STS).

Methods: This was a multinational, open-label, randomized (1:1) Phase 3 study of Evo (300 mg/m²) IV on Days 1 and 8 (21-day cycle) with D on Day 1 (75 mg/m²). Pts on Evo plus D could receive Evo alone after Cycle 6. Key eligibility: locally advanced unresectable or metastatic STS, intermediate or high grade, no prior chemotherapy for advanced disease, ECOG 0/1, measurable disease at baseline, adequate hematological and hepatic functions. Pts were randomized 1:1 to receive Evo + D or D alone (range 18-89); 54% female; 57% ECOG 0; 36% leiomyosarcoma, 17% liposarcoma, 12% lipoma, 7% synovial sarcoma.

Results: From Sept 2011 to Jan 2014, 640 pts were randomized (317 Evo + D, 323 D); 621 pts were treated. Baseline characteristics were balanced: Median age 59 years (range 18-89); 54% female; 57% ECOG 0, 36% leiomyosarcoma, 17% liposarcoma, 12% undifferentiated pleomorphic sarcoma; 89% metastatic, 11% locally advanced disease. Median cycles were 6 and D dose intensity was 99% through 6 cycles, in both arms. Single agent Evo was continued in 46% of pts on Evo + D after Cycle 6. OS endpoint was not reached (HR = 1.06 [95% CI: 0.88-1.29]) with median OS of 14.8 months with Evo + D vs. 19.0 months with D. RR was 28.4% on Evo + D vs. 18.3% for D (odds ratio of 1.69 [95% CI: 1.28 – 2.28, p < 0.003]). Median PFS was 6.3 months on D vs. 6.0 months on D, HR = 0.85 (95% CI: 0.70-1.03, p = 0.099). Most common grade 3/4 AEs were anemia (13%), neutropenia (33%) and leukopenia (18%). Febrile neutropenia was noted in 18% of pts on Evo + D and 11% on D. AEs leading to death were 2.6% on Evo + D and 1.0% on D. AEs leading to discontinuation were 8.3% on Evo + D and 6.2% on D.

Conclusions: The combination of Evo + D did not improve OS compared to D. The safety profile was consistent with that previously reported.

Clinical trial identification: NCT01440088 First Received: September 20, 2011 Legal entity responsible for the study: Threshold Pharmaceuticals Funding: Threshold Pharmaceuticals Disclosure: W. Tap: Receipt of grants/research support: Sarcoma Foundation of America Receipt of honoraria or consultation fees: Novartis, EMD Serono, Eli Lilly, Daiichi Sankyo, Janssen. R.L. Jones: Consulting role with Eisai Pharmamar Merck Adaptimmune Immune design Immodulon Daiichi Lilly Pfizer. S.P. Chawla: Daiichi Sankyo, Janssen. R.L. Jones: Consulting role with Eisai Pharmamar Merck America Receipt of honoraria or consultation fees: Novartis, EMD Serono, Pharmamar. All other authors have declared no conflicts of interest.

EMD Serono. T. Pearce: Employee for Threshold Pharmaceuticals. S. Kroll: Employee of Threshold Pharmaceuticals, who is company leading development of TH-302 and also stock ownership in Threshold Pharmaceuticals. All other authors have declared no conflicts of interest.

Results of a prospective randomized phase III T-SAR trial comparing trabectedin vs best supportive care (BSC) in patients with pretreated advanced soft tissue sarcoma (STS)

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Background: Trabectedin (T) has demonstrated single-agent activity in patients (pts) with pretreated ASTS and was approved in 2007 in Europe in this indication. With the exception of a study in translocation-related sarcomas (Kawai, 2015), T was never compared to BSC in a randomized study in pts with all sarcoma histotypes. The efficacy, safety and quality of life of T vs BSC as second or later treatment line were evaluated in pts with ASTS in a multicenter French Sarcoma Group (FSG) trial.

Methods: The study included adult pts ≥18 years of age with histologically proven ASTS who progressed after at least one anthracycline-containing regimen (≥3 previous chemotherapy lines), stratified by L-STS and non L-STS, and non-L-STS, with ≥1 measurable baseline lesion as per RECIST v.1.1, WHO performance status score 0-1, adequate hematological and hepatic functions. Pts were randomized 1:1 to receive either (1.5 mg/m²) a 14-day every 3 weeks (E) or BSC until disease progression (PD). This study met its first endpoint as a preplanned PFS analysis showed a 2.58, p = 0.003. Median PFS was 6.3 months on T vs 6.0 months on BSC, HR = 0.78 (95% IC: 0.59-1.03, p = 0.074). In the L-STS cohort, the median PFS in the T and BSC arm were 1.4 m and 5.8 m (HR: 0.33, 95% IC: 0.17-0.62, p = 0.0003), respectively, whereas in the non-L-STS group the median PFS was 1.3 m and 2.6 m (HR: 0.49, 95% IC: 0.26-0.94, p = 0.03).

Conclusions: This study met its first endpoint as a preplanned PFS analysis showed a significant improvement in median PFS with trabectedin over BSC in pts with pretreated ASTS of multiple histologies.

Clinical trial identification: 2014-003176-23 Legal entity responsible for the study: Gustave Roussy Institute Funding: Pharmamar Disclosure: A. Le Cesne: Honoraria from Novartis, Pfizer, Pharmamar, Lilly. J-Y. Blay: Honoraria from Roche, Novartis, Pfizer, Lilly, Bayer, Pharmamar. I.L. Ray-Coquard: Honoraria from Roche, Novartis, Pharmamar, Merck. All other authors have declared no conflicts of interest.

Background: Since 2009 a network of 26 reference centres for sarcoma patients (pts) in France was designated by the French National Cancer Institute. The outcome of the 26,883 pts discussed in these 26 NETSARC multidisciplinary tumour boards (NMTB) is presented.

Methods: The NETSARC database includes pts characteristics, treatment and diagnosis procedures, progression and survival. Soft tissue, visceral, and bone sarcomas represented 57% (6,940/12,282), 21% (2,571/12,282), and 5% (625/12,282) respectively. Individual NETSARC centres managed a median of 404 (range 92-2,974) pts in 5 yrs.

Results: 13,845 women (52%) and 13,038 men (48%), with a median age of 60y (range 0-101) were included. Leiomyosarcoma, GIST, liposarcoma, and undifferentiated pleomorphic sarcoma were the most frequent histotypes. 11% pts had metastases at diagnosis. Only 40% of pts had a reference centre prior to first treatment. The median follow-up of the series is 26 months (range 6-590). At 24 months, local and metastatic relapse rates were not significantly different. Overall survival rate at 24 months is 87%.

Conclusion: The comprehensive approach of NETSARC is associated with improved survival of pts with various types of sarcomas. Further prospective studies are required to determine the impact of a reference centre prior to initial treatment.

Legal entity responsible for the study: The Institute of Cancer Research Funding: Wellcome Trust UK

Disclosure: All authors have declared no conflicts of interest.
Anti-PD1 therapy with nivolumab in sarcoma

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Background: Manipulation of immune checkpoints such as CTLA4 or PD-1 with targeted antibodies, has recently emerged as an effective anticancer strategy in multiple malignancies. Sarcomas are a heterogeneous group of diseases in need of more effective treatments. Different subtypes of soft tissue and bone sarcoma have been shown to express the PD-1 ligand.

Methods: We retrospectively analyzed a cohort of patients (pts) with relapsed metastatic sarcomas, who were treated with nivolumab provided under a patient assistance program from the manufacturer.Pts underwent CT or PET/CT imaging at baseline and after at least 4 doses of nivolumab; RECIST criteria were used for response assessment.

Results: Twenty-five pretreated pts with metastatic soft tissue (STS, N = 22) or bone sarcoma (N = 3), received IV nivolumab 3mg/kg every 2 weeks. Median age was 58 (24-78), male female was 11:14, ECOG PS was 0 in 21 pts, 1 in 4 pts; the median number of previous treatments was three (0-6); the median number of nivolumab cycles was eight; seventeen pts concomitantly received the tyrosine kinase inhibitor pazopanib at 800mg daily. The most common side effect was grade 1 or 2 LFT elevations (10 pts, 8 of them receiving pazopanib); grade 3-4 toxicity occurred in 6 pts and included grade 4 pneumonitis, grade 3 colitis, grade 3-4 LFT elevations and grade 3 anemia. Twenty pts receiving at least 4 cycles thus far were evaluable for response. We observed three partial responses (PR) one de differentiated chondrosarcoma, one prostatic epithelial sarcoma (on pazopanib) one and osteosarcoma of the maxillary sinus (on pazopanib), eight pts had stable disease (SD); one intimal sarcoma, one synovial sarcoma, one alveolar soft part sarcoma, one osteosarcoma, on malignant peripheral nerve sheath tumor and three leiomyosarcomas, eight had progression of disease (PD); three leiomyosarcoma, one synovial sarcoma, one mesenchymal chondroblastoma, one de differentiated liposarcoma, one desmoplastic small round cell tumor and one undifferentiated pleomorphic sarcoma. Clinical benefit (PR + SD) was observed in 11 pts.

Conclusions: Collectively, our data provide a rationale for further exploring the efficacy of nivolumab and other checkpoint inhibitors in soft tissue and osteosarcoma.

Legal entity responsible for the study: Luca Pauza

Funding: New York University

Disclosure: All authors have declared no conflicts of interest.

Subgroup analysis of leiomyosarcoma (LMS) patients (pts) from a phase 3, open-label, randomized study of eribulin (ERI) versus dacarbazine (DTIC) in pts with advanced liposarcoma (LPS) and LMS

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Background: Different subtypes of soft tissue sarcomas have a significant impact on therapy and outcomes. For example, sarcoma of bone and soft tissue exhibit differences in patient age, histology and behavior. We aimed to determine whether these differences impact the efficacy and safety of ERI in LMS pts.

Methods: Pts aged ≥18 yrs with histologically confirmed advanced LMS, and from 3 geographic regions, were included. Pts with ECOG status ≤2 and ≥2 prior systemic treatment regimens, including an anthracycline, were randomized 1:1 to ERI (1.4 mg/m² IV, on Day [D] 1 and D8) or DTIC (850, 1000, or 1200 mg/m² IV, on D1) every 21D until disease progression. OS, progression free survival (PFS), and safety were compared with LPS pts treated with DTIC (13.0 mo vs. 8.4 mo). OS was improved with ERI (13.2 mo vs. 11.2 mo respectively, HR = 0.77 [95% CI 0.54 - 1.09]), with non-uterine disease (177 pts; 14.4 vs 10.84 mo; HR = 0.79 [95% CI 0.59 - 1.07]), and enrolled in geographic region ≥2 (175.2 µg/mL; Cmin1 ≥ 62.8 µg/mL). A consistent OS benefit was observed across the 3 upper quartiles. The survival models reflected the greater OS benefit. ECavg50 and ECmin150 corresponded to the median Olara exposure (Cavg 134 µg/mL; Cmin1 66.1 µg/mL) and the median Olara exposure (Cavg 134 µg/mL; Cmin1 66.1 µg/mL) across quartiles of Olara serum levels and a time-to-event (survival) model with a constant baseline hazard and a Hill function to describe the effect of Olara. The rate of treatment-emergent adverse events (TEAEs) was compared across quartiles of Olara exposure.

Results: The MCC analysis using both Cavg and Cmin1 showed a benefit in PFS above the median Olara exposure (Cavg ≥ 175.2 µg/mL; Cmin1 ≥ 62.8 µg/mL), with patients progressing earlier in the lowest quartile (Cavg < 134.4 µg/mL; Cmin1 < 62.8 µg/mL). A consistent OS benefit was observed across the upper 3 quartiles. The survival models for PFS/OS yielded similar findings. The Olara half-maximum effective concentration (Cavg) and trough serum concentration after cycle 1 (Cmin1). The PFS/OS data were analyzed using a matched case-control (MCC) analysis across quartiles of Olara serum levels and a time-to-event (survival) model with a constant baseline hazard and a Hill function to describe the effect of Olara. The rate of treatment-emergent adverse events (TEAEs) was compared across quartiles of Olara exposure.

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Conclusions: The exposure-response relationship of Olara for progression free survival (PFS), overall survival (OS) and safety.

Methods: PFS/OS, pharmacokinetic (PK) and safety data from the 66 patients who received Olara on the phase 2 study were analyzed. The effect of Olara serum levels was explored using average serum concentration (Cavg) and trough serum concentration (Cmin1) every 21D until disease progression. These results prompted a loading dose strategy in the ongoing phase 3 STS trial.

Clinical trial identification: NCT01189964

Legal entity responsible for the study: Eli Lilly and Company


Exposure-response of olaratumab for survival outcomes and safety when combined with doxorubicin in soft tissue sarcoma (STS) patients

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Background: Olaratumab (Olara), a recombinant human IgG1 monoclonal antibody, selectively binds human PGDFRα. Olara plus doxorubicin (Dox) improved survival vs Dox in a Phase 2 sarcoma trial (NCT01189964). We characterized the exposure-response relationship of Olara for progression free survival (PFS), overall survival (OS) and safety.

Methods: PFS/OS, pharmacokinetic (PK) and safety data from the 66 patients who received Olara on the phase 2 study were analyzed. The effect of Olara serum levels was explored using average serum concentration (Cavg) and trough serum concentration (Cmin1) every 21D until disease progression. These results prompted a loading dose strategy in the ongoing phase 3 STS trial.

Clinical trial identification: NCT01189964

Legal entity responsible for the study: Eli Lilly and Company

Background: Oral encoctytes imatinib (IMN), sunitinib (SNN) and pazopanib (PZN) show a high interpatient variability in pharmacokinetics. For IMN, SNN and PZN a relationship between plasma exposure and treatment outcome has been established, which supports the rationale for dose optimization of these drugs. The aim of this study was to monitor how many patients reached adequate trough levels (Cmin) after dose optimization in daily practice.

Methods: An observational study was performed in a cohort of patients treated with IMN, SNN or PZN of whom multiple drug levels were measured between August 2012 and April 2016. Patients’ characteristics were collected by reviewing medical records. Drug levels were measured using LC-MS/MS and Cmin were estimated using the algorithm of Wang et al. Result: 396 trough levels were determined in 109 patients. Median sample frequency per patient was 3. During the first measurement only 38% of patients showed Cmin within the predefined target range. 52% of the patients showed a drug level below and 10% above target range. Dose interventions were proposed in 72 (66%) patients and implemented in 41 (38%) patients. In 35 out of 41 patients (85%) dose interventions led to an adequate Cmin. Eventually, 64% of the total cohort reached an adequate Cmin.

Conclusion: This study shows that dose optimization is an effective tool to reach adequate Cmin for patients treated with IMN, SNN and PZN. Initially, only 38% of patients had an adequate Cmin. Of the patients undergoing dose intervention 85% reached an adequate Cmin. Plasma exposure awareness might add to the improvement of efficacy and toxicity of patients treated with IMN, SNN and PZN.

Legal entity responsible for the study: Radboudumc

Funding: Radboud University Medical Center

Disclosure: All authors have declared no conflicts of interest.

Table: 1403PD

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<th>Sunitinib</th>
<th>Pazopanib</th>
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<td>75</td>
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<td>Cmin Measurement</td>
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<td>Last</td>
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<tr>
<td>Adequate Cmin (%)</td>
<td>29 (41)</td>
<td>42 (60)</td>
<td>7 (10)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Patients with interventions n (%)</td>
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<td>Patients with adequate Cmin after intervention n (%)</td>
<td>15 (79)</td>
<td>12 (75)</td>
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<td>1 (10)</td>
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</table>

Optimizing the dose in cancer patients treated with imatinib, sunitinib and pazopanib

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Conclusions: Regorafenib is an active drug. None of the tested genes (VEGFR1, VEGFR2, VEGFR3, FGFR1, KIT, PDGFRB, RAF1, RET1, TIE2, TP53 and CH1P2 genes) was found to be predictive for PFS or OS. Combinatorial analysis and further subgroup testing is currently ongoing.

Clinical trial identification: EudraCT 2012-005743-24

Legal entity responsible for the study: Sarcoma Platform Austria & French Sarcoma Study Group

Funding: Bayer

Disclosure: T. Brodowicz: Lecture fee: Roche, Amgen, Bayer, Novartis, Pharmacia, Eisai Advisory Board: Amgen, Bayer, Novartis, Eisai. O. Mir: Consultant for: Astra-Zeneca, Amgen, Bayer, RMS, Novartis, Pfizer and Roche. J-Y. Blay: Advisory Board: Roche, Novartis, Bayer, MSD, Lilly, Ipsen, Decipher, Bayer. Corporate-sponsored Research: Roche, Novartis, Bayer, MSD, Lilly, Pharmacia. A. Le Cesne: Honoraria: Novartis, Pharmacia, Lilly, Pfizer. N. Penel: Research grant from Bayer HealthCare. All other authors have declared no conflicts of interest.

Circulating vascular endothelial growth factor (VEGF) as prognostic factor of progression-free survival in patients with advanced chordoma receiving sorafenib: An analysis from a phase II trial of the French Sarcoma Group (GSF/ GETO)

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Background: Patients with advanced chordoma are often treated with tyrosine kinase inhibitors without any predictive factor to guide decision. We report herein the ancillary analysis of the predictive values of circulating proangiogenic biomarkers among patients included in the Angionext phase II trial and treated with sorafenib (NCT 00874874).

Methods: Patients were treated with sorafenib 800 mg/day for 9 months, unless earlier occurrence of progression or toxicities. Six biomarkers (s-Selectin, VEGF, VEGF-C, placental growth factor (PlGF), Thrombospondin, Stem Cell Factor (SCF)) were measured in 2 blood samples at baseline (day 1: D1) and day 7 (D7). Changes in levels of circulating biomarkers were analyzed with paired Student t-test. Prognostic value of biomarkers for progression-free survival (PFS) was analyzed using univariate Cox model.

Results: From May 2011 to January 2014, 26 out of 27 patients included in the original study were sampled, including 17 men and 9 women, with a median age of 64 years. The primary sites were sacrum (20, 78%), mobile spine and skull base (3 each, 11%). 50% of patients had metastatic disease (13/26). After central radiological review, the 9-month PFS rate was 72% (95% Cl: 45.9-87.7). During sorafenib treatment, a significant increase in PFG (18.4 vs 43.8 pg/mL, p < 0.001) was noted along with a significant decrease in VEGF (0.7 vs 1.0 ng/mL, p = 0.07). There was no significant change for the 4 other biomarkers. VEGF at D7 >1.04 ng/mL (HR = 12.5, 95% Cl: 1.37-114, p = 0.025) and VEGF at D7 >1.36 ng/mL versus 27.8% (95%-CI: 1.3-68.4) when >1.36 ng/mL were significant predictors of PFS.

Conclusion: Consideration of circulating proangiogenic biomarkers in patients with advanced chordoma receiving sorafenib might improve clinical decision-making.

References:


First line therapy with aldoxorubicin and 14 days continuous infusion of ifosfamide/ mesna in metastatic or locally advanced sarcomas: a phase I-II study

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Background: Aldoxorubicin (A) has demonstrated superior anti-tumor efficacy and lack of cumulative cardiac toxicity in multiple studies. A is doxorubicin (D) with a linker which rapidly binds in vivo to albumin after iv administration. We studied the combination of A administered on Day 1 with continuous infusion (CI) of ifosfamide/ mesna (I-M) days 1-14, in patients with sarcomas to evaluate efficacy and toxicity.

Methods: A total of 27 patients were enrolled between Dec 2013 and Nov 2014. The planned sample size was not reached due to accrual rate. The median age was 29.5 years (range, 23 - 36 years). Among six patients, one achieved partial response (ORR 16.7%) and five patient showed stable disease. One patient with metastatic ASPS was documented with TFE3 overexpression with metastatic ASPS due to resistance to conventional chemotherapy. Considering these results, a large phase I-II trial of A+I-M was not feasible.

Conclusions: First line therapy with aldoxorubicin in patients with metastatic soft part sarcoma appears promising and warrants further development.

First line therapy with aldoxorubicin and 14 days continuous infusion of ifosfamide/mesna in metastatic or locally advanced sarcomas: a phase I-II study

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Conclusions: First line therapy with aldoxorubicin in patients with metastatic soft part sarcoma appears promising and warrants further development.
Tolerability of modified gemcitabine/docetaxel (split-dose) in patients with advanced soft tissue sarcomas

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Background: Soft tissue sarcomas (STS) encompass a wide group of malignancies that pose a therapeutic challenge when diagnosed at advanced stages. The combination of gemcitabine/docetaxel (GD) has shown meaningful activity in this setting and is considered a valid therapeutic option. Nevertheless, GD is associated with significant toxicities and modifications are frequently used in clinical practice in an attempt to enhance the tolerability.

Methods: We assembled a retrospective cohort of patients (pts) with advanced STS treated with the conventional GD (cGD): gemcitabine (900-1000mg/m2) given on day 1 and day 8 + docetaxel (75mg/m2) given on day 8 only or modified GD (mGD) with "split-dose" docetaxel (30-37.5mg/m2) given on days 1 and 8. The primary endpoint was to compare the incidence of grade 3/4 adverse events (AE) and use of G-CSF; additional outcomes included rate of admission to the hospital, progression free survival (PFS) and overall survival (OS). Survival curves were estimated using the Kaplan-Meier method. The association of clinical/pathological or treatment variables and survival was investigated.

Results: We identified 76 pts treated with cGD (n = 32; 42.1%) or mGD (n = 44; 57.9%). Sixty-six pts (90.8%) had high grade tumors and most frequent histologies were leiomyosarcoma (n = 20; 26.3%) and undifferentiated pleomorphic sarcoma (n = 21; 27.6%).Pts receiving mGD were more likely to have and ECOG ≥2 (p = 0.05). Grade 3/4 AE occurred in 13 (40.6%) of pts treated with cGD and 21 (47.7%) of pts treated with mGD (p = 0.539). Use of G-CSF occurred in 28 pts (87.5%) treated with cGD and 23 pts (52.3%) treated with mGD (p = 0.001). Rates of admission to the hospital and dose reductions were similar between groups (p = 0.107 and p = 0.941, respectively). Survival intervals were comparable between groups: median PFS was 2 months (mo) for pts treated with cGD and 3 mo for mGD (p = 0.8); median OS was 13 months (95% Cl: 6.5-11.3) in AS, respectively.

Conclusions: Despite being used for patients with poor performance status, mGD resulted in similar efficacy, incidence of grade 3/4 AE and lower G-CSF use in comparison to cGD. This finding is particularly relevant for cost contingency in settings with limited resources.

Legal entity responsible for the study: Instituto do Câncer do Estado de São Paulo Funding: Instituto do Câncer do Estado de São Paulo Disclosure: All authors have declared no conflicts of interest.
Response rate was 64% (558 respondents; 418 soft tissue, 140 bone). Most patients drawn from respondents to National Cancer Patient Experience Surveys Sarcoma UK, the only all sarcoma charity in the UK, patient advocates and sarcoma clinicians. In England, questionnaires were dispatched by post to a sample of 900 patients drawn from respondents to National Cancer Patient Experience Surveys 2010-14 (fieldwork January-March 2015): Here we focus on the diagnostic pathway.

**Results:** Response rate was 64% (558 respondents, 418 soft tissue, 140 bone). Most common presenting symptoms were painless lump (41% (n = 229), ‘something else’ 31% (n = 173) and lump increasing in size 30% (n = 166). 31% (n = 64) of bone sarcoma patients presented with pain. Younger patients (16-34 years) were more likely to report painful lumps, older patients (85+ years) reported increasing size. Of all patients, 18% (n = 96) presented >6 months after first noting symptoms. 24% of bone sarcoma vs 16% of soft tissue sarcomas; 17% of bone sarcomas waited >1 year. General Practitioners (GP) referred 34% for tests and 33% to hospital specialists. Of all respondents who visited their GP, 97% were referred for another condition, and 18% were told their symptoms were not serious and to come back (9%) or not come back (9%) if symptoms persisted. Of patients attending Accident & Emergency departments, 25% were not treated appropriately; 10% of patients (younger than more old) were treated for another condition.

**Conclusions:** Delay in presentation is a significant factor, which may adversely impact long-term outcome and quality of life. Additionally, frequent misdiagnosis highlights the low level of suspicion, education and knowledge in primary and secondary healthcare. These data will encourage initiatives to improve awareness among the public and healthcare professionals.

**Legal entity responsible for the study:** Sarcoma UK.

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**Disclosures:** All authors have declared no conflicts of interest.
Possible prognostic value of local immunity cellular factors in primary and recurrent soft tissue sarcomas

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Background: The purpose of the study was to analyze prognostic value of some cellular factors of immunologic microenvironment in soft tissue sarcomas (STS) for the development of an effective response to treatment for primary and recurrent tumors.

Methods: 24 patients (13 women and 11 men aged 35 years and older) with primary (12) and recurrent (12) soft tissue sarcoma (G1-G4TNM0M0, mostly poorly differentiated G3 tumors) underwent surgical removal of tumors with the following adjuvant chemotherapy and radiotherapy. Tissues of tumors and peritumoral area obtained during the surgery were homogenized; percentage of lymphocytes (T-, B-, NK, NK- DP, DN, T-reggs) was determined using FACSanalyz III (Becton-Dickinson) by flow cytometry.

Results: Patients were divided into 4 groups according to the results of clinical observation: group A – primary tumors, marked treatment effect; group B – primary tumors, no treatment effect; group C – recurrent tumors, marked treatment effect; and group D – recurrent tumors, no treatment effect. Retrospective assessment of local immunity statuses of patients revealed a number of differences in lymphocyte content. Patients with primary STS showed significant prognostic value of CD16/56+ level in tumor tissue (12.2 ± 1.6% in marked treatment effect and 6.1 ± 1.2% without an effect (p < 0.05). Levels of NK- and NKT-cells were twice higher in peritumoral tissues in group A compared to group B. Absence of treatment effect in recurrent STS was associated with an increased content of DN cells in tumor tissue (9.3 ± 2.2% in group D vs. 5.5 ± 0.8% in group C, p < 0.05).

Conclusions: A high local level of DN-lymphocytes, especially in recurrent tumors, and decreased content of NK-cells in primary tumors can be considered as prognostic factors for effectiveness of treatment for soft tissue sarcomas.

Legal entity responsible for the study: Rostov Research Institute of Oncology

Funding: Ministry of Health of the Russian Federation

Disclosure: All authors have declared no conflicts of interest.

Disclosure: All authors have declared no conflicts of interest.

Long-term safety of regorafenib (REG) in advanced gastrointestinal stromal tumours (GIST): updated safety data of the phase 3 GRID trial

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Background: The GRID trial showed that REG improves progression-free survival (primary endpoint; data cutoff January 2012) versus placebo in patients (pts) with advanced GIST after failure of imatinib and sunitinib (Lancet 2013; 381: 295). At progression, placebo pts could cross over to REG treatment and pts randomized to REG could continue to receive REG. We present an updated safety analysis of pts in GRID who were treated with REG at any time (any REG; AR) and of the subgroup who had long-term REG (LTR) treatment (>1 year).

Methods: The 199 randomized pts (n = 133 REG; n = 66 placebo) 58 placebo pts crossed over to REG. At the time of this analysis (June 2015), a total of 190 pts (95%) were treated with AR and 75 (38%) had LTR. Starting dose was REG 160 mg once daily for the first 3 weeks of each 4-week cycle.

Results: The LTR group tended to have a better ECOG status (PS0: AR 57%/LTR 69%; PS1: AR 43%/LTR 31%). A similar proportion were treated with AR and 75 (38%) had LTR. Starting dose was REG 160 mg once daily for the first 3 weeks of each 4-week cycle.

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Annals of Oncology


1417P Prediction of long-term survival in metastatic gastrointestinal stromal tumour: analysis of a large, single-institution patient cohort

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Background: Treatment of metastatic gastrointestinal stromal tumour (GIST) has improved considerably after the introduction of imatinib. A subset of patients become long-term survivors, and a more precise outcome prediction could improve clinical decision-making.

Methods: Patients diagnosed with metastatic GIST from 1995 to 2013 were identified from the sarcoma database at Oslo University Hospital. Clinical data were prospectively registered in the database and supplemented with retrospective review of medical records. Factors associated with survival were analysed using Kaplan-Meier curves, log-rank test and uni- and multivariate Cox regression analysis.

Results: One-hundred thirty-three patients with metastatic GIST were identified, and 115 were included in the final study cohort. First-line treatment with imatinib was given to 111 patients, two received pazopanib and two never received systemic treatment. Second-line treatment was administered to 35 patients and third-line therapy to 19 patients. Median overall survival (OS) was 6.9 years (95% CI 3.6-8.3). After a median follow-up of 9.0 years, 52 patients (43%) were still alive. Factors associated with long-term survival in univariate analysis were good baseline performance status (ECOG ≤1; p < 0.001), young age (p = 0.022), oligometastatic disease (≤5 metastases; p < 0.001), maximum tumour diameter ≤5 cm (p = 0.001), surgery for metastatic disease (p = 0.005), radical surgery of the primary tumour (p < 0.001), normal baseline haemoglobin level (p = 0.046), normal baseline albumin level (p = 0.001) and normal baseline neutrophil count (p = 0.032). In multivariate analysis, good performance status and oligometastatic disease were the only factors associated with outcome. Five-year and 10-year OS for patients with oligometastatic GIST were 89% and 71%, respectively, compared to 38% and 20% for patients with more disseminated disease.

Conclusions: In the present cohort oligometastatic disease and good performance status were the most important predictors of long-term survival. Patients with oligometastatic disease had an excellent outcome, and may be regarded as a separate category among patients with metastatic GIST.

Legal entity responsible for the study: N/A

Funding: Rakel and Otto Kr Bruun's Legacy, Oslo University Hospital Foundation and the Norwegian Cancer Society

Disclosure: All authors have declared no conflicts of interest.

1418P The role of neoadjuvant imatinib therapy of patients with primary locally advanced GIST

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Background: Percutaneous biopsy of gastrointestinal tumors is contraindicated; that is the role of neoadjuvant imatinib therapy of gastrointestinal stromal tumors (GIST). The purpose was to study the role of neoadjuvant and adjuvant imatinib therapy (at least for 3 years) in patients with primary locally advanced GIST.

Methods: The role of neoadjuvant imatinib therapy of patients with primary locally advanced GIST was evaluated. In the study, 133 patients with metastatic GIST were identified, and 141 patients with primary locally advanced GIST were included. Neoadjuvant imatinib therapy was given to 111 patients, two received nilotinib and two never received systemic treatment. The remaining 35 patients were treated with adjuvant imatinib therapy. In the patients with 5-years of adjuvant therapy, diseases progression was not noted. During neoadjuvant therapy disease progression has been registered in two patients. The median time of neoadjuvant imatinib therapy was 11 months (from 3 to 24 months). Neoadjuvant imatinib therapy increased the rate of R0 (14 pt – 82.4%) and organ-sparing (12 pts – 70.6%) resections.

Conclusions: The optimal approach in patients with locally advanced GIST is combined surgical treatment with neoadjuvant and adjuvant (at least for 3 years) imatinib therapy.

Legal entity responsible for the study: N. N. Blokhin Russian Cancer Research Center, Moscow

Funding: N. N. Blokhin Russian Cancer Research Center, Moscow

Disclosure: All authors have declared no conflicts of interest.

1419P Prospective analysis in GIST patients on the role of alpha-1 acid glycoprotein (AGP) in imatinib exposure

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Background: For imatinib, a relationship between systemic exposure and clinical outcome has been suggested. Importantly, imatinib concentrations are not stable and decrease over time for which several mechanistic hypotheses have been suggested. One theory assumes that reduction of the inflammatory syndrome, due to decreasing tumor burden or due to resolving surgery effects, leads to lower levels of the acute phase protein alpha-1 acid glycoprotein (AGP). Consequently, imatinib is proposed to be bound less to this protein, causing a larger proportion of the drug to be available for elimination, which in turn leads to lower systemic exposure over time. Here, we investigated if a decrease in AGP is the main cause of the decrease in imatinib exposure.

Methods: We prospectively measured imatinib trough concentrations (Cmin) in 31 patients with GIST, at 1, 3, and 12 months from start of imatinib treatment. At the same time points AGP was measured. Correlations were tested using Pearson’s correlation coefficient and geometric means were compared using ANOVA. The study was approved by the local institutional review board (protocol number MEC13-203) and written informed consent was obtained from all individual participants included in the study.

Results: Overall, imatinib Cmin and AGP were correlated (r = 0.607; p < 0.001; Pearson’s correlation), but the correlation between change in AGP between the first two time points and change in imatinib Cmin was less strong (r = 0.358; p = 0.001; Pearson’s correlation). Moreover, AGP concentrations did not fluctuate significantly over time (p = 0.160; ANOVA), which contradicts the theory that reduced inflammatory syndrome leads to lower AGP concentrations in GIST patients.

Conclusions: We show that systemic AGP concentrations are not likely to be a key player in the decrease of systemic imatinib exposure over time. As long as the inter-individual changes in imatinib exposure remain unexplained, researchers should standardize the sampling times of imatinib in order to be able to compare the clinical applicability of TDM.

Legal entity responsible for the study: Erasmus MC Cancer Institute

Funding: Erasmus MC Cancer Institute

Disclosure: All authors have declared no conflicts of interest.

1420P ANNOUCE 2: An open-label phase 1b, and a randomized, double-blind phase 2 study of olaratumab with gemcitabine plus docetaxel in the treatment of patients with advanced soft tissue sarcoma (STS)


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Background: While doxorubicin has been the mainstay of treatment for decades, in more recent years gemcitabine plus docetaxel has emerged as an effective treatment in metastatic STS. The platelet-derived growth factor receptor alpha (PDGFRα) antibody olaratumab in combination with doxorubicin demonstrated a significant improvement of overall survival over doxorubicin alone in patients with advanced STS in a randomized phase 2 study (NCT01185964). Since some patients may not be appropriate candidates for doxorubicin-based chemotherapy, or have received prior anthracycline treatment, exploring the efficacy and safety of olaratumab with gemcitabine plus docetaxel is of considerable interest.

Trial design: ANNOUCE 2 (NCT02659020) is a multicentre Phase 1b/2 study of olaratumab in combination with gemcitabine and docetaxel in patients with advanced...
to detect an improvement in progression-free survival (PFS) rate at 4 months from 50% to 80% with a one-sided 15% significance level. Pts randomized to the placebo arm may cross-over to cabozantinib at the time of progression. This trial is a cooperation between European Organisation for Research and Treatment of Cancer (EORTC), Cancer Research UK (CRUK) and National Cancer Institute (NCI, US) and is part of the International Rare Cancers Initiative (IRCIC). Primary objective: PFS rate at 4 months according to RECIST 1.1 Secondary objectives: PFS, OS, Overall Survival, Safety, Response Rate and duration of response. Study status: The first pts from EORTC (as a participating countries) was randomized in Feb 2015. As of 6 May 2016, 15 and 5 pts have been registered and randomized after central pathology confirmation of HGUS, respectively. CRUK has started recruitment in May 2016 and NRG Oncology in US is expected to start in October 2016.

**Clinical trial identification:** NCT number: NCT01979393, EudraCT: 2013-000762-11

**Legal entity responsible for the study:** European Organisation for Research and Treatment of Cancer (EORTC)

**Funding:** European Organisation for Research and Treatment of Cancer (EORTC)

**Disclosure:** All authors have declared no conflicts of interest.

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### A randomized double-blind phase II study evaluating the role of maintenance therapy with cabozantinib in high grade undifferentiated uterine sarcoma (HGUS) after stabilization or response to doxorubicin +/- ifosfamide evaluating surgery or in metastatic first line treatment

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**Background:** HGUS accounts for 6% of all uterine sarcomas and has a very poor prognosis. Most patients (pts) die of recurrent disease within 1 year of diagnosis. Treatment recommendations for advanced stage include chemotherapy with anthracyclines +/- ifosfamide, although data for the efficacy of these agents in this histologic subtype are very limited. Recently vascular invasion reported to be a driver of the progression for such sarcoma subtype suggesting anti-angiogenesis and so cabozantinib (VKGFR2/c-MET inhibitor) potentially active for HGUS.

**Trial design:** This randomized phase II double-blinded trial aims to measure the role of maintenance therapy with cabozantinib in HGUS after stabilization (SD) or docetaxel (75 mg/m² Day 8) in a 21-day cycle. The primary objective is to determine a dose of olaratumab that may be safely administered in combination with cabozantinib and docetaxel in patients with advanced or metastatic STS. Secondary objectives are to evaluate the safety and toxicity profile, pharmacokinetics, and immunogenicity of olaratumab in combination with cabozantinib and docetaxel, and to document any antitumor activity. After the optimal dose of olaratumab in combination with cabozantinib and docetaxel has been determined, the Phase 2, randomized, double-blind, placebo-controlled part of the study will open to enrolment (in approximately December 2016). The study began in March 2016; planned enrollment for the 1b phase is approximately 30 patients.

**Clinical trial identification:** NCT02659020

**Legal entity responsible for the study:** Eli Lilly and Company


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### Phase II, singlearm, nonrandomized, and multicenter clinical trial of regorafenib (REG) as a single agent in the frontline setting for patients with metastatic and/or unresectable KIT/PDGFR wild-type GIST. A GEIS and ISG study

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**Background:** Approximately 10-15% of adults with GIST lack KIT or PDGFR mutations. This KIT/PDGFR wild-type (wt) GIST is considered a separate pathological entity and is highly clinically heterogeneous. Because most KIT/PDGFR wt-GISTs do not respond to imatinib, new treatment approaches are needed. REG is an oral multikinase inhibitor that has been shown to improve progression-free survival (PFS) and disease control rate (DCR) vs placebo in patients with advanced GIST progressing after failure of imatinib and sunitinib (Demetri et al. Lancet 2013). This study was designed to assess the effectiveness of REG in patients with metastatic and/or unresectable KIT/PDGFR wt-GIST in the first-line setting.

**Trial design:** Patients ≥18 years of age with histologically confirmed unresectable and/or metastatic KIT/PDGFR wt-GIST do not respond to imatinib, new treatment approaches are needed. REG is an oral multikinase inhibitor that has been shown to improve progression-free survival (PFS) and disease control rate (DCR) vs placebo in patients with advanced GIST progressing after failure of imatinib and sunitinib (Demetri et al. Lancet 2013). This study was designed to assess the effectiveness of REG in patients with metastatic and/or unresectable KIT/PDGFR wt-GIST in the first-line setting.

**Trial design:** The first pts from EORTC (6

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### Clinical trial identification:** NCT number: NCT01979393, EudraCT: 2013-000762-11

**Legal entity responsible for the study:** European Organisation for Research and Treatment of Cancer (EORTC)

**Funding:** European Organisation for Research and Treatment of Cancer (EORTC)

**Disclosure:** All authors have declared no conflicts of interest.
SCLC

**Randomized phase 2 study of investigational aurora A kinase (AAK) inhibitor alisertib (MLN8237) + paclitaxel (P) vs placebo + P as second line therapy for small-cell lung cancer (SCLC)**


**Background:** Alisertib, a selective AAK inhibitor, showed single-agent antitumor activity in preclinical in vivo SCLC models and was synergistic with P in this setting. We report the efficacy (PFS, OS, ORR) and safety from this study.

**Methods:** Pts ≥18 y with SCLC relapsed ≤180 d after standard first-line platinum-based chemotherapy were randomized 1:1 to alisertib 40 mg + P 60 mg/m2 (Arm A) or matched placebo + P 80 mg/m2 (Arm B) in 28-d cycles with alisertib taken orally twice daily on d 1, 8, 15, 17, and paclitaxel given intravenously on d 1, 8, 15. Pts were stratified using an interactive voice response system (IVRS) based on type of relapse following frontline platinum (sensitive vs resistant/refractory) and presence/absence of brain metastases at baseline. Protocol Amendment 2 corrected the definition for relapse per standard guideline, and the stratification factors were corrected accordingly. Primary endpoint was PFS assessed by stratified log-rank test.

**Results:** 178 pts were randomized (89/89) Arm A/B; median age 62/62 y. The analysis of PFS using IVRS stratification favored Arm A (median 101 vs 66 d) with HR 0.77, 95% CI 0.57–1.06; p = 0.113. The analysis for PFS using the corrected stratification factors again favored Arm A with HR 0.72, 95% CI 0.52–1.04; p = 0.038. Median OS was 186 vs 165 d, with HR 0.93, 95% CI 0.65–1.34; p = 0.714 and ORR was 22% vs 18%, disease control rate 58% vs 46%, stable disease 55% vs 49%, and progressive disease 15% vs 26%. Pts received a median of 3 (1–11) cycles. Rates of AEs were higher in Arm A.

<table>
<thead>
<tr>
<th><strong>Table: 1423D</strong> Safety population</th>
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<tbody>
<tr>
<td><strong>Arm A</strong></td>
</tr>
<tr>
<td>n = 87</td>
</tr>
<tr>
<td>AE (≥20%)</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Stomatitis</td>
</tr>
<tr>
<td>Appetite</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Dryness</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
</tr>
<tr>
<td>Drug-related Grade ≥3 AEs</td>
</tr>
<tr>
<td>Drug-related serious AEs</td>
</tr>
<tr>
<td>AEs leading to treatment</td>
</tr>
<tr>
<td>discontinuation</td>
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</tbody>
</table>

Conclusions: Alisertib + P shows favorable PFS over placebo + P with both corrected and IVRS stratification. A similar favorable trend was observed for OS and ORR. The alisertib + P arm showed higher rates of AEs and discontinuation due to AEs. Further analyses are pending.

**Disclosure:** T.K. Owonikoko: Consulting; Medivation, Novartis, Lilly, Amgen; Research funding; Novartis, Stencentrix, BMS, Colgene, AstraZeneca, Takeda, Regeneron, G1 Therapeutics, Calithera, AbbiVie. E. Sheldon-Wangi, D. Huetter: Employment (Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited); stock ownership: Takeda Pharmaceutical Company Limited; Corporate-sponsored research; Takeda-sponsored clinical trial. All other authors have declared no conflicts of interest.

**Clinical trial identification:** NCT02038647; EudraCT 2013-003713-18 (Clinical Trial Protocol Cl4018 Protocol Amend 2 2015-01-23)

**Legal entity responsible for the study:** Millennium Pharmaceuticals, Inc.

**Funding:** Millennium Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

**Abstracts**
Clinical activity, safety and predictive biomarkers results from a phase Ia atezolizumab (atezo) trial in extensive-stage small cell lung cancer (ES-SCLC)

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Background: Most patients (pts) with ES-SCLC receive platinum-based chemotherapy with etoposide, however median survival is ≤ 1 y, and new options are needed. Here we assess the safety and clinical activity of the cancer immunotherapy atezo (anti-PDL1) as monotherapy in ES-SCLC.

Methods: ES-SCLC pts received atezo IV q3w at 15 mg/kg or 1200 mg as part of a Ph Ia study (NCT01375842). Due to protocol amendments the first 5 pts were PD-L1 selected and the subsequent 12 were not PD-L1 selected. Initially treatment was to last up to 1 y though retreatment at PD was allowed. Later pts were treated until loss of clinical benefit. RECIST v1.1 and irRC assessments were used. PD-L1 expression was centrally evaluated using the VENTANA SP142 IHC assay. Tfeffor (Teff) gene signature (CD8a, GZMA, GZMB, EOMES, CX3C9, CXCL10, TBX21) and PD-L1 mRNA was measured (ichip).

Results: As of Dec 15, 2015, 17 pts with a minimum follow-up of 6 mo, were therapy/ efficacy evaluable. 65% were male; 88% were ECOG PS 1. Median age was 63 y (range 44-80), and pts were heavily pretreated (65% ≥ 3 prior therapies). 65% pts had grade 1-5 treatment-related AEs most often fatigue (24%). There were 8 related G3-5 AEs in 3 pts, including 1 G3 pneumonitis leading to treatment discontinuation and 1 G5 hepatic failure. Confirmed ORR by RECIST was 6% (1 PR with DOR of 7 mo, also irPR by iRC) and 24% by irRC. 4/17 pts received atezo for ≥ 6 mo, 2 of these for ≥ 12 mo. 1 irPR pt stopped atezo per protocol after 1 y and remained in irPR for an additional 1 y until PD. Upon retreatment, the patient again derived benefit and is still on atezo as of Jan 2016. RECIST v1.1 and irRC assessments were used. PD-L1 expression was lateralized overall, consistent with published data. A trend toward greater clinical benefit was seen for Teff gene signature and PD-L1 mRNA.

Conclusions: These initial results in ES-SCLC demonstrate a tolerable safety profile with no new safety signals for atezo. Atoezo also showed encouraging single-agent activity, based on the duration of clinical benefit in a subset of patients. Further studies of atezo in ES-SCLC are planned.

Clinical trial identification: NCT01375842

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: L.V. Sequist: Consulting: uncompensated consulting with BI, Clovis, Merrimack, Novartis, Genentech; Taisho, and consulting with AZ, Arixid Research; BI, Clovis, Merrimack, Merck, Novartis, Genentech Advisory Board Research funding for trials: Boehringer Ingelheim, OncoMed, Millennium, Onyx, J. Gilbert: Research funding: for clinical trials, not salary); from AZ, Merck, Pfizer, Threshold, M. Gordon: Research funding from Genentech and Roche for research activities which is provided to the institution. P.R. Conkling: Research funding. UniOncology Research S.J. Antonia: Honoraria: BMS, AstraZeneca, Advisory boards: Genentech, Merck Consulting: BMS, AstraZeneca Research: MedImmune Travel: BMS, AstraZeneca. B. Liu: D.S. Shames, A. Lopez-Chavez: Genentech employee. C. O’Hear: Genentech Employee. Stocker/other ownership: Genentech/ Roche. Research funding from Genentech, M. Fasso: Genentech Employee and Aduro Bio, Inc. All other authors have declared no conflicts of interest.

A phase 1/2 trial of a monoclonal antibody targeting fucosyl GM1 in relapsed/refractory small cell lung cancer (SCLC): Safety and preliminary efficacy

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Background: Fucosyl-GM1 (Fuc-GM1), a ganglioside with abundant yet restricted expression on the cell surface of SCLCs, is a potential target for therapeutic approaches. Here we present preliminary results from a Phase 1/2 study of BMS-986012, a
first-in-class fully human IgG1 monoclonal antibody with enhanced ADCC that specifically binds to FcγRIIIA, for the treatment of SCLC.

Methods: Patients (pts) with relapsed/refractory SCLC after at least one line of prior therapy were enrolled. BMS-986012 was administered IV at flat doses of 70, 160, 400, and 1000 mg every 3 weeks (wk) during dose escalation. Pharmacokinetics (PK) and anti-drug antibodies (ADA) were assessed during cycle 1.

Results: Twenty-nine pts were treated across all doses. Median age was 63 yr (range: 26–81). 55% were female; 95% had a smoking history. Pts had received up to five lines of prior therapy; 52% had one prior line; 48% had 2 or more two prior lines. Nine pts were platinum refractory (>5 mo from end of first line therapy to progression). No dose limiting toxicities or treatment-related grade 4 or 5 adverse events occurred. Treatment-related adverse events occurring in >10% of pts were pruritus, decreased appetite, and rash. Preliminary PK analysis suggests a linear dose-exposure relationship (Table). No ADAs were detected.

Table: 1427PD Summary of Single Dose Exposures of BMS-986012

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>AUC (0-504 hr)</th>
<th>Cmax (mg/mL)</th>
<th>Geom. Mean (CV) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>4543 (31)</td>
<td>28 (28)</td>
<td>(36)</td>
</tr>
<tr>
<td>160</td>
<td>8544 (23)</td>
<td>74 (125)</td>
<td>(26)</td>
</tr>
<tr>
<td>400</td>
<td>19642 (47)</td>
<td>145 (26)</td>
<td>(23)</td>
</tr>
<tr>
<td>1000</td>
<td>44677 (23)</td>
<td>348 (29)</td>
<td>(23)</td>
</tr>
</tbody>
</table>

One confirmed complete response (CR; duration 53 wk; 70 mg dose level) and one confirmed partial response (PR; duration 17 wk; 400 mg dose level) were observed. Stable disease (SD) was reported in 4 pts. The CR and 2 SD occurred among the 9 platinum refractory pts.

Conclusions: BMS-986012 demonstrates a manageable safety profile and resulted in objective responses in relapsed SCLC, including platinum refractory refractory pts. Preliminary PK analysis showed dose-proportional and linear increase in exposure with moderate to high variability. Dose expansion is currently ongoing at 400 and 1000 mg.

Clinical trial identification: NCT02324734

Legal entity responsible for the study: Sponsored by Bristol-Myers Squibb

Funding: Sponsored by Bristol-Myers Squibb

Disclosure: Q.-S.C. Chu: Personal fees from BMS and Lilly (advisory boards), Novartis (advisory board and consultancy), and Astra Zeneca, Merck (advisory and consultancy). Grants and personal fees from BI (Research Grant and advisory board) L. Krug: Grants from Bristol-Myers Squibb, during the conduct of the study, other from Bristol-Myers Squibb, outside the submitted work. C. Rudin: Personal fees from Bristol Myers Squibb, Celgene, Novartis, Medivation, and Merck, outside the submitted work. D. Lathers: Employee & Shareholder at BMS. P. Basciano: Personal fees from Bristol-Myers Squibb, outside the submitted work as a Study Sponsor. P.M. Fracasse: Employee of BMS. P. Phillips: Employee of Bristol-Myers Squibb. N. Ready: Personal fees from Bristol Myers Squibb, Celgene, Novartis, Medivation, and Merck, outside the submitted work. All other authors have declared no conflicts of interest.

1428P | Phase II/II study of induction chemotherapy using carboplatin plus irinotecan and sequential thoracic radiotherapy (TRT) for elderly patients with limited-stage small cell lung cancer (LD-SCLC): The final results of TORG 0604


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Background: The role of irinotecan for elderly patients with LD-SCLC has been unclear, and the timing of TRT combined with chemotherapy has not been fully evaluated.

Methods: Patients aged ≥70 years with untreated, measurable, LD-SCLC, performance status (PS) 0-2, and adequate organ function were eligible. Treatment consisted of induction with carboplatin on day 1 and irinotecan on days 1 and 8, every 21 days for 4 cycles, and sequential TRT (54 Gy in 27 fractions). Carboplatin doses were based on

AUC of 4 and 5 (levels 1 and 2, respectively), with a fixed irinotecan dose (50 mg/m2). Primary objectives of the phase II study were efficacy, adverse events, and feasibility.

Results: Forty-one patients were enrolled (median age 75 years (range 70-86 years), males 31, PS 0/1/2, n = 22/18/1). The number of patients with carboplatin dose-limiting toxicities at levels 1 (n = 6) and 2 (n = 6) were 1 (grade 3 hypertension) and 2 (grade 4 thrombocytopenia), respectively. The phase II trial was expanded to 29 additional patients receiving the level 1 carboplatin dose. The median number of chemotherapy cycles was 4 (range 1-4), and the median radiation dose was 54 Gy (range 36-60). Toxicities were generally mild. There were 5 complete and 30 partial responses (response rate 90%). With a median follow-up of 80.4 months (n = 41), the median progression-free and overall survival times were 12.5 and 27.5 months, respectively.

Conclusions: Induction chemotherapy of carboplatin plus irinotecan and sequential TRT was well tolerated and effective for elderly patients with LD-SCLC. Additional confirmatory studies are warranted.

Legal entity responsible for the study: Thoracic Oncology Research Group (TORB)

Funding: Nippon Kayaku, Taiho, Lilly, Sanofi, Chugai, Astra Zeneca, Daichi Sankyo, Shionogi

Disclosure: All authors have declared no conflicts of interest.
A Phase III study of atezolizumab with carboplatin plus etoposide in patients with extensive-stage small cell lung cancer (IMPower133)


Background: The current standard first-line treatment for the majority of patients (pts) with extensive-stage small cell lung cancer (ES-SCLC) is platinum-based chemotherapy with etoposide. Despite initial response rates ranging from 50% to 70%, median survival remains < 1 year (Angelici et al. 2018). Atezolizumab (atezo) is an anti-PD-L1 agent that inhibits PD-L1/PD-1 signaling and restores anti-tumor T-cell activity. Atezo mono-therapy shows promise efficacy and safety in many tumor types, including SCLC. ORR by RECIST v1.1 is 6% (1/17), ORR by irRC is 4% (1/25), 1432Tip Immune surveillance reactivation to improve overall survival in small cell lung cancer (SCLC): The randomized IMPULSE study


Background: The immune surveillance reactivator lefitolimod (MGN1703), a DNA-based Toll-like receptor 9 (TLR9) agonist, was compared to placebo in metastatic CRC (mCRC) patients with disease control after standard induction chemotherapy in the double-blind randomized phase 2 IMPULSE study. Lefitolimod showed a superior effect over placebo in exploratory analyses of pretreatment characteristics that identified patients most likely to benefit from lefitolimod. A study in small cell lung cancer (SCLC) patients, IMPULSE, was designed to present this preliminary evidence of efficacy in a new, high-mortality-and-unmet-need indication.

Trial design: Trial characteristics: IMPULSE is a randomized, international, multicenter, open-label trial to assess the effect of TLR9-mediated immune surveillance reactivation on overall survival (OS) in extensive disease (ED) SCLC patients. Secondary endpoints include PFS, response rates, safety, and quality of life (QOL). The baseline stratification factors neuron-specific enolase (NSE) and activated NKT cells are prospectively assessed. 103 patients with objective tumor response following 4 cycles of platinum-based first-line induction therapy were randomized to receive either lefitolimod switch-maintenance therapy or local standard of care in a 3:2 ratio. Upon relapse, patients are receiving appropriate second-line therapy. All patients take part in a comprehensive immune monitoring plan that will evaluate cytokines and chemokines in serum, and the activation status of various immune cell populations. A study in small cell lung cancer (SCLC) patients, IMPULSE, was designed to present this preliminary evidence of efficacy in a new, high-mortality-and-unmet-need indication.

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supportive care

1433C

Phase 3 efficacy and safety trial of proposed pegfilgrastim biosimilar MYL-1401H vs EU-neulasta® in the prophylaxis of chemotherapy-induced neutropenia

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Background: MYL-1401H is a proposed pegfilgrastim biosimilar to the reference product EU-Neulasta®, based on physicochemical characterization, in vitro bioassays, toxicokinetics (TK), pharmacokinetics (PK), and pharmacodynamics (PD) studies.

Methods: This is a phase 3, multicenter, randomized, double-blind, parallel-group trial of MYL-1401H vs EU-Neulasta® in patients with newly diagnosed Stage II/III breast cancer who were to receive docetaxel, doxorubicin, and cyclophosphamide anti-cancer chemotherapy planned every 3 weeks for 6 chemotherapy cycles. A total of 194 patients were randomized in a 2:1 ratio to receive 6 mg/0.6 mL of either MYL-1401H or EU-Neulasta® on Day 2 of each cycle. The primary efficacy endpoint was the duration of severe neutropenia (DSN) in Cycle 1 as defined by absolute neutrophil count (ANC) < 0.5 x 10^9/L in the per-protocol population. The sample size to provide 90% power to declare that MYL-1401H is comparable to Neulasta® in the analysis of duration of severe neutropenia (DSN) in cycle 1 will be calculated based on the expected 95% confidence interval (CI) of the least squares mean difference between the DSNs falls wholly within an equivalence region defined as [–1, +1] day. A sensitivity analysis with the intent-to-treat population was also carried out.

Results: The mean ± SD DSN in the MYL-1401H and EU-Neulasta® groups were 1.2 ± 0.93 and 1.2 ± 1.10, respectively. The 95% CI of least squares means difference (–0.285 day, 0.298 day) was within [–1, +1] day range, that was also corroborated by the Cochran-Mantel-Haenszel test with absolute neutrophil count (ANC) as a stratification factor. The proportion of patients with ANC nadir, and duration of post-nadir recovery were comparable too. The overall safety profile of MYL-1401H was similar to EU-Neulasta® with bone pain, an expected AE, as the most frequently reported treatment related TEAE.

Conclusions: MYL-1401H demonstrated equivalent efficacy to EU-Neulasta® in the prophylaxis of chemotherapy induced neutropenia in patients with breast cancer. MYL-1401H was generally well tolerated and there were no particular safety concerns identified with the biosimilar compared to EU-Neulasta®. A Phase 3 trial of MYL-1401H vs EU-Neulasta® in patients with breast cancer is currently ongoing.

Clinical trial identification: EudraCT Number: 2014-00324-27

Legal entity responsible for the study: Mylan GmbH

Funding: Mylan GmbH

Disclosure: C.G. Waller: Member of advisory board of Mylan. E. Pennella: Mylan Employee and stocks of Mylan. M. Bronchud: Member of consultant/advisory board of Mylan. M. Kothe: Member of consultant/advisory board of Mylan. M. Bazkowsky: Currently an employee of Mylan. In addition, financial relationship with employer in the form of stock options, restricted stock units, and shares of Mylan in retirement account. M. Kothe: Full-time employee of Biocon Research Limited. A. Barve: Mylan full-time employee and stock in Mylan. All other authors have declared no conflicts of interest.
Exploration of the heterogeneity of moderately emetogenic chemotherapy on response to fosaprepitant in a randomized phase 3 trial

C. Weinstein1, K. Jordan2, S. Green3

Background: A single-day triple-antiemetic fosaprepitant (FA) regimen demonstrated superiority to a standard 3-day regimen for preventing chemotherapy induced nausea and vomiting (CINV) in subjects receiving non-anthracycline and cyclophosphamide (AC)-based moderately emetogenic chemotherapy (MEC). However, the impact of MEC etiogenicity and duration of chemotherapy warrants exploration.

Methods: This was a phase 3, global, randomized, double-blind, parallel-group study in adults scheduled to receive an IV dose of ≥ two MEC agents on treatment day 1. Subjects were randomly assigned 1:1 to a control or FA regimen. The control regimen consisted of 8 mg oral ondansetron, 20 mg dexamethasone, and IV saline as placebo before the first dose of MEC on day 1, and 8 mg oral ondansetron 8 hours before the first dose, and every 12 hours on days 2 and 3. The FA regimen consisted of the same dose of oral ondansetron on day 1, along with 12 mg dexamethasone and a single dose of 150 mg IV FA before the first dose of MEC on day 1, with no additional prophylactic antiemetic beyond day 1. Primary endpoint was complete response (CR; no vomiting or rescue medication) in the delayed phase (0 to 120 hours following MEC).

Results: Overall, 1000 subjects were included in the intent-to-treat population (FA: n = 502; Control: n = 498). The primary endpoint was met (P < 0.001; FA vs control).

Conclusion: A single-day FA regimen is effective for preventing CINV in subjects receiving non-AC MEC with or without carboplatin and in both single- and multiple-chemotherapy regimens.

Clinical trial identification: ClinicalTrials.gov: NCT01954749; release: August 26, 2015

Legal entity responsible for the study: This work was supported by Merck & Co., Inc., Kenilworth, NJ.

Funding: This work was supported by Merck & Co., Inc., Kenilworth, NJ.

Disclosure: C. Weinstein, S. Green: Employee and stockholder of Merck & Co., Inc. K. Jordan: honoraria for consultancy from Merck Sharp & Dohme (MSD), Merck & Co., Inc. S. Green: employee and stockholder of Merck & Co., Inc. K. Jordan: Honoraria for consultancy from Merck Sharp & Dohme (MSD), Merck & Co., Inc. W. Liang: Employee of Merck & Co., Inc. S. J. Noga: Honoraria from Millenium and consultant or in an advisory role for Agena and Millenium (now Takeda Oncology). B.L. Rapoport: Consultant or in an advisory role for and received payment for travel, accommodations or expenses from MSD and Tesaro and also received payments for participation on speaker’s bureau for MSD and Roche. All other authors have declared no conflicts of interest.
Methods: CINV outcomes and risk factor data were obtained from 1198 patients enrolled in 1 of 5 non-interventional prospective cohort studies. For the cycle-based risk model, disease and treatment factors that were potential predictors of CINV were identified at baseline and after each cycle of CT. Factors with a p-value < 0.05 following a CT cycle were retained and included in a generalised estimating equations (GEE) regression analysis. A risk scoring algorithm (range: 0–32) derived from the final model coefficients was then developed. As a final step, the predictive accuracy of the algorithm was assessed via a receiver operating characteristic curve (ROC) analysis.

Results: Over 4197 cycles of CT, 42.2% of patients experienced ≥2 CINV. Ten risk factors were retained in the final model (eg, age <60, earlier CT cycles, early stage disease, expectation of N&V, history of morning sickness, hours of sleep the night before CT, N&V in the prior cycle). The ROC analysis indicated good predictive accuracy with an area under the curve of 0.71 (95% CI 0.69 – 0.73). Prior to each cycle, a risk score cut point of ≥16 units would optimize the model sensitivity (Table); patients with a score ≥16 units would be considered at high risk for developing ≥2 CINV.

Table: 1438PD

<table>
<thead>
<tr>
<th>Score cut point</th>
<th>CINV incidence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8</td>
<td>12.5%</td>
<td>100%</td>
<td>0%</td>
<td>1.0</td>
</tr>
<tr>
<td>8 to &lt; 12</td>
<td>13.6%</td>
<td>99.8%</td>
<td>1.2%</td>
<td>1.01</td>
</tr>
<tr>
<td>12 to &lt; 16</td>
<td>23.1%</td>
<td>97.9%</td>
<td>10.7%</td>
<td>1.10</td>
</tr>
<tr>
<td>16 to &lt; 20</td>
<td>43.7%</td>
<td>87.4%</td>
<td>43.8%</td>
<td>1.42</td>
</tr>
<tr>
<td>20 to &lt; 24</td>
<td>57.6%</td>
<td>51.2%</td>
<td>75.7%</td>
<td>2.11</td>
</tr>
<tr>
<td>24 to &lt; 28</td>
<td>72.8%</td>
<td>18.8%</td>
<td>94.8%</td>
<td>3.60</td>
</tr>
<tr>
<td>≥ 28</td>
<td>87.9%</td>
<td>2.1%</td>
<td>99.8%</td>
<td>9.08</td>
</tr>
</tbody>
</table>

Conclusions: Risk of CINV varies according to number of cycles administered, type of CT, N&V in the prior cycle, and patient factors. The application and continued refinement of this prediction tool will be an important source of patient-specific risk information that will allow the personalization of antiemetic therapy.

Legal entity responsible for the study: Augmentus Pharma Consulting

Funding: Helsinn Healthcare


1440P

Efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients with gastrointestinal and colorectal cancers

P. Navari1, K. Jordan2, B.L. Rapoport3, I. Schnidt4, M. Chae5, S. Arora6, D. Powers7, L. Schwartzberg8

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Background: Rolapitant (VARUBI®) is a selective, long-acting neurokinin-1 receptor antagonist (RA) for the prevention of chemotherapy-induced nausea and vomiting (CINV). Rolapitant effectively prevented grade ≥3 CINV in patients receiving highly or moderately emetogenic chemotherapy (HEC, MEC). While MEC and HEC regimens are commonly used to treat pts with gastrointestinal and colorectal cancers (GC/CRC), very few studies have evaluated the effectiveness of a neurokinin-1 RA regimen in these pts. We assessed the incidence of CINV and efficacy of rolapitant in a subset of pts with GC/CRC.

Methods: This is a post hoc analysis of 3 similarly designed, randomized, placebo-controlled trials. Pts with cancer of the esophagus, stomach, colon/rectum, or anus received a single oral dose of 180 mg oralrolapitant or placebo prior to HEC or MEC. All pts received a 5-hydroxytryptamine type 3 (5-HT3) RA and dexamethasone (active control). The HEC studies included cisplatin, and the MEC study carboplatin, oxaliplatin, irinotecan, epirubicin, and docetaxel. Endpoints included complete response (CR; no emesis and no use of rescue medication), no emesis, no nausea (maximum visual analogue scale [VAS] ≤ 5 mm), no significant nausea (maximum VAS ≤ 25 mm) and complete protection (CP; no emesis, no use of rescue medication, and no significant nausea) in the overall (0–120 h), acute (<24 h), and delayed (>24–120 h) phases.

Results: Out of 188 GC/CRC pts, 101 pts received rolapitant and 87 received active control. Pts treated with rolapitant had significantly higher rates of CR, no nausea, no emesis, and CP in the overall phase (P < 0.05). Rolapitant was well-tolerated and overall incidence of treatment-emergent adverse events comparable in both groups.

Conclusions: Addition of rolapitant to 5-HT3 RA and dexamethasone therapy significantly improved CR, no nausea, no emesis, and CP in pts with GC/CRC receiving emetogenic chemotherapy.

Table: 1440P

<table>
<thead>
<tr>
<th>Endpoint, %</th>
<th>Pooled HEC/MEC</th>
<th>Rolapitant (n = 101)</th>
<th>Control (n = 87)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Overall phase</td>
<td>Complete response</td>
<td>73.3</td>
<td>48.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No emesis</td>
<td>77.2</td>
<td>56.3</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>No significant nausea</td>
<td>69.3</td>
<td>58.6</td>
<td>0.128</td>
<td></td>
</tr>
<tr>
<td>No nausea</td>
<td>52.5</td>
<td>31.0</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Complete protection</td>
<td>64.4</td>
<td>41.4</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Clinical trial identification: NCT01500226, NCT01499849, NCT01500213

Legal entity responsible for the study: TESARO, Inc.

Funding: TESARO, Inc.

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Efficacy and safety of rolapitant in the prevention of chemotherapy-induced nausea and vomiting (CINV) in elderly patients

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Background: Although older patients (pts) may have less CINV compared with younger ones, preventative treatments with a good safety profile are needed. This analysis evaluates the efficacy and safety of the long-acting neurokinin-1 receptor antagonist (RA) rolapitant according to pt age (<65 vs ≥65 years).

Methods: In 3 double-blind studies, pts receiving highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) were randomized 1:1 to treatment with 180 mg oral rolapitant or placebo prior to chemotherapy, always with a single dose of 180 mg oral rolapitant or placebo before chemotherapy. All pts received a standard 5-HT3 RA + dexamethasone (active control). Treatment-emergent AEs were recorded in all pts receiving BCRP substrate drugs and compared between the rolapitant and control arms.

Results: CR rates, no emesis, and CP were significantly higher with rolapitant (P < 0.05) in overall phase in both age groups in the 2 pooled HEC studies and 1 MEC study. Time to first emesis or use of rescue medication was longer with rolapitant than with placebo in both age groups administered HEC or MEC. Rolapitant was well-tolerated with a similar percentage of pts reporting ≥1 treatment-related adverse event in both groups.

Conclusions: Rolapitant provides protection against CINV in elderly pts who were administered emetogenic chemotherapy.

Clinical trial identification: NCT01500226, NCT01499849, NCT01500213

Legal entity responsible for the study: TESARO, Inc.

Funding: TESARO, Inc.

Disclosure: M.S. Aapro: Consultant/Advisor (CA), Research Funding (RF), Speakers Bureau (SB): Amgen, Novartis, Roche, J&J; Honoraria & Expert Test: Bureau (SB): Helsinn, Hospira, Sandoz, PFM; CA/SB: Teva, Tesaro, Vifor Pharma; CA: Disclosure:

M.S. Aapro: Consultant or Advisor (CA), Research Funding (RF), Speakers Bureau (SB): Amgen, Novartis, Roche, J&J; Honoraria & Expert Test: Bureau (SB): Helsinn, Hospira, Sandoz, PFM; CA/SB: Teva, Tesaro, Vifor Pharma; CA: Disclosure:

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M.S. Aapro: Consultant/Advisor (CA), Research Funding (RF), Speakers Bureau (SB): Amgen, Novartis, Roche, J&J; Honoraria & Expert Test: Bureau (SB): Helsinn, Hospira, Sandoz, PFM; CA/SB: Teva, Tesaro, Vifor Pharma; CA: Disclosure:

Table: 1442P

<table>
<thead>
<tr>
<th>BCRP substrates* (n rolapitant; n control)</th>
<th>Most common TEAs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin (147; 148)</td>
<td>Durebra (23.0); fatigue (20.3); constipation (17.6)</td>
</tr>
<tr>
<td>Docetaxel (291; 303)</td>
<td>Fatigue (19.2); alopecia (13.7); neutropenia (11.0)</td>
</tr>
<tr>
<td>Fluorouracil (224; 230)</td>
<td>Alopecia (10.4); constipation (10.4); fatigue (9.1)</td>
</tr>
<tr>
<td>Irinotecan (19; 34)</td>
<td>Durebra (20.6); alopecia (11.8); constipation (8.8)</td>
</tr>
</tbody>
</table>

*Partial list

Conclusions: Rolapitant + 5-HT3 receptor antagonist + dexamethasone was safe and well-tolerated in pts receiving concomitant BCRP substrate chemotherapy agents.

Clinical trial identification: NCT01500226, NCT01499849, NCT01500213

Table: 1441P

<table>
<thead>
<tr>
<th>Pooled HEC</th>
<th>&lt;65 y</th>
<th>≥65 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall phase (0-120 h)</td>
<td>Rolapitant (n = 397)</td>
<td>Control (n = 395)</td>
</tr>
<tr>
<td>Complete response</td>
<td>68.0</td>
<td>58.0</td>
</tr>
<tr>
<td>No emesis</td>
<td>72.5</td>
<td>61.6</td>
</tr>
<tr>
<td>No significant nausea</td>
<td>70.8</td>
<td>63.6</td>
</tr>
<tr>
<td>No nausea</td>
<td>50.9</td>
<td>39.9</td>
</tr>
<tr>
<td>Complete protection</td>
<td>61.5</td>
<td>53.2</td>
</tr>
<tr>
<td>MEC &lt;65</td>
<td>Overall phase (0-120h)</td>
<td>Rolapitant (n = 495)</td>
</tr>
<tr>
<td>Complete response</td>
<td>67.5</td>
<td>63.0</td>
</tr>
<tr>
<td>No emesis</td>
<td>77.6</td>
<td>63.6</td>
</tr>
<tr>
<td>No significant nausea</td>
<td>67.1</td>
<td>65.7</td>
</tr>
<tr>
<td>No nausea</td>
<td>41.2</td>
<td>38.5</td>
</tr>
<tr>
<td>Complete protection</td>
<td>59.6</td>
<td>51.9</td>
</tr>
</tbody>
</table>
Chemotherapy-induced nausea and vomiting (CINV) is a common problem in cancer patients undergoing chemotherapy. Although antagonists for 5-HT3 and NK-1 receptors and corticosteroids are effective in the prevention of CINV, patients undergoing highly emetogenic chemotherapy (hematopoietic cell transplantation, cisplatin-based chemotherapy) have a high risk of severe CINV. Rikkunshito (RKT), a Japanese herbal medicine, is widely prescribed in Japan to treat various gastrointestinal disorders, and has been reported to recover the decreases in food intake and serum ghrelin levels caused by cisplatin treatment. However, its clinical efficacy in highly emetogenic chemotherapy is still insufficient.

A randomized phase II study was conducted to evaluate the antiemetic efficacy of RKT (7.5 g/day for 14 days) with standard antiemetics (granisetron, aprepitant and dexamethasone) compared with the control group (57.9% vs 35.3%, P = 0.175). Furthermore, CCR in the delayed phase endpoint CCR in the overall phase was significantly higher in the RKT group than in the control group (17 in the RKT group, 17 in the control group) were included in efficacy analysis. The primary endpoint was complete control rate (CCR) in the overall phase (0-120 hours after CDDP administration), and secondary endpoints were complete response rate ( CCR) in the overall phase (0-120 hours after CDDP administration), and secondary endpoints were complete response rate (CCR), partial response rate (PRR), and complete response rate (PCR).

Conclusions: Efficacy of rikkunshito, a Japanese herbal medicine, on nausea, vomiting and anorexia in patients with uterine cervical or corpus cancer treated with cisplatin and paclitaxel was demonstrated in this randomized phase II study. However, further controlled trials are needed to confirm the results.
Malnutrition in 822 Irish cancer patients undergoing chemotherapy: prevalence and impact on quality of life and survival

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Background: Malnutrition is common in the oncology setting and negatively impacts on clinical outcomes1. The aim of this study was to assess the nutritional status of this cohort and the impact of malnutrition on quality of life (QOL) and survival.

Methods: A cross sectional study of adult cancer patients undergoing chemotherapy between 2012-2015 was conducted. A survey was devised, incorporating clinical, nutritional, biochemical and QOL data (EORTC). Nutritional status was evaluated using cancer cachexia (CC) diagnostic criteria2 and CT assessment of body composition3. Cox proportional hazards model was used for survival analysis.

Results: 822 patients with solid tumours participated in the study, 60% were male with a median age of 64 years (IQR 56-71 years). 44% had a BMI < 25kg/m2, while only 4.6% had visible malnutrition (BMI < 18.5kg/m2). 36% of patients had lost >5% body weight in 6 months, 44% had CC, 40% were sarcopenic, 47% had myosteatosis, 24% had both. In terms of QOL, weight loss was significantly associated with a poorer global QOL score, as well as worse physical, role, emotional and social function scores (all p < 0.005) and higher symptoms such as fatigue, nausea and vomiting, pain, appetite and diarrhoea (all p < 0.005). Sarcopenia, myosteatosis and CC were all significantly associated with reduced survival, with the highest risk of mortality seen in those with both myosteatosis and sarcopenia. Median survival was 589 days (95% CI 391-774 days) vs. 1001 days in those without both conditions (95% CI 746-1256 days; log rank p = <0.001). On multivariate analysis, controlling for age, sex, performance status, treatment intent and BMI, patients with both conditions had increased risk of mortality (HR 1.45, 95% CI 1.12-1.87, p = 0.004).

Conclusions: Malnutrition and abnormal body composition are common in Irish cancer patients, but are masked by excessive adiposity. Malnutrition can adversely impact on patients QOL and survival. 1. Martin L, Birdsell L, MacDonald N et al. (2013) J Clin Oncol, 31 (12):1539-1547. 2. Fearon K, Strasser F, Amler SD et al. (2011) Lancet Oncol, 12 (9):489-95

Legal entity responsible for the study: University College Cork

Funding: Science Foundation Ireland (SFI) under Grant Number SFI/12/RC/2273

Disclosure: All authors have declared no conflicts of interest.

Incidence and clinical outcomes of febrile neutropenia in adult cancer patients with chemotherapy using Korean nationwide health insurance database

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Background: Febrile neutropenia (FN), treatment-associated bone marrow suppression often renders cancer patients prone to life-threatening infections. The aim of this study was to evaluate episodes of FN in patients with stomach, colorectal, lung and breast cancer, and identify the incidence and the trend for admission rate, costs, and factors affecting mortality.

Methods: Using nationwide claim data from the Korean Health Insurance (NHI) database, all new admissions to the hospitals for FN were selected. Prescription data of granulocyte colony-stimulating factors and antibiotics were also collected from the NHI database. We evaluated the incidence of FN and the mortality-related clinical factors in the adult cancer patients who received cytotoxic chemotherapy from January 2004 to December 2013.

Results: Total 313,316 patients were searched as newly diagnosed adult cancer with age over 18 years. Among these, 44,412 patients were hospitalized for FN during chemotherapy. The incidence of FN is 15.9% in lung cancer, 15.3% in stomach cancer, 13.3% in breast cancer, and 9.5% in colorectal cancer, respectively. The trends of incidence are increasing for 10 years, but mean hospitalization days are decreasing. Admission rate to intensive care unit is highest in lung cancer (15.2%). Mean total cost of FN is 3,115 euro per one admission. In-hospital mortality is 19.3% in lung cancer, 15.1% in stomach cancer, 8.9% in colorectal cancer, and 5.9% in breast cancer. Age and sex are risk factors for in-hospital mortality for all cancer type.

Conclusions: FN is increasing but length of hospitalization is decreasing in Korea. In-hospital mortality of FN was overall 12.9% and showed decreasing trends. Factors associated with increased mortality in hospitalized patients with FN are old age and sex.

Legal entity responsible for the study: National health insurance service

Funding: National health insurance service

Disclosure: All authors have declared no conflicts of interest.
Background: Previous studies showed that anticonvulsants might improve the prevention of chemotherapy-induced nausea and vomiting (CINV). Pregabalin is a structural derivative of the inhibitory neurotransmitter γ-aminobutyric acid. It binds potently to the calcium channels, resulting in a reduction of the release of several neurotransmitters including glutamate, noradrenaline, serotonin, dopamine, and substance P. Some of these transmitters are involved in the pathophysiology of nausea and vomiting. To our knowledge, the antiemetic role of pregabalin hasn’t been investigated yet.

Methods: We performed a phase II randomized, double-blind, placebo-controlled trial to investigate if pregabalin could improve the complete control of nausea and vomiting (primary end point). We enrolled eighty two chemotherapy-naive patients, scheduled to receive moderately and highly emetogenic chemotherapy. All patients received IV ondansetron 8 mg, dexamethasone 10 mg and ranitidine 50 mg before chemotherapy on day 1 and oral dexamethasone 4 mg, bd, on days 2 and 3. Patients were randomly assigned to take pregabalin 75 mg or placebo, bd, from the night before chemotherapy to day 5. All patients received a diary to record the moment of failure, considered in this study as any episode of emesis, moderate or severe nausea or use of rescue medication. We used chi2 test to evaluate the difference of proportions between groups.

Results: The overall complete response were 53.7 vs. 51.2% (p = 0.82). The overall complete response were 53.7 vs. 48.8% respectively in the granisetron and metoclopramide group for nausea (0 vs 95%, p < 0.0005) and vomiting (0 vs 64%, p < 0.001). No statistically significant difference was detected between granisetron and metoclopramide group for incidence of CINV was statistically significant lower in the granisetron group both for nausea (9 vs 89%, p < 0.0005) and vomiting (0 vs 64%, p < 0.001). No statistically significant difference was detected between gransertron and metoclopramide group for constipation (38 vs 18%) and bowel occlusion (10 vs 10%).

Conclusions: Our results showed that transdermal granisetron is more effective in CINV prevention and as safe as oral metoclopramide in terms of rate of constipation and bowel obstruction in patients affected by mCRC receiving TMZ. Thus transdermal granisetron might represent a standard in CINV prevention in this setting.

**Clinical trial identification:** EudraCT 2012-002766-13

**Legal entity responsible for the study:** Fondazione Policlinico “A. Gemelli”, Rome

**Funding:** Fondazione Policlinico “A. Gemelli”, Rome

**Disclosure:** All authors have declared no conflicts of interest.
Background: Primary prophylaxis with G-CSF is not indicated in patients with solid tumors treated with chemotherapy with low or intermediate risk (<20%) of febrile neutropenia (FN). However, a group of them will develop clinically relevant neutropenic events (CRNE), defined as having a dose reduction, dose delay, treatment interruption, FN or hospital admission due to neutropenia. Identification of clinical baseline characteristics that correlate with CRNE development could optimize neutropenia management.

Methods: The purpose of this prospective, multicenter study was to develop and validate a risk model to predict the occurrence of CRNE in patients with solid tumors receiving chemotherapy with low or intermediate risk of FN (<20%). Data on clinical, biochemical and tumors parameters was collected prospectively from 420 patients at ten institutions. The sample was randomly divided into training (N = 320) and validation sample (N = 100). Risk factors for CRNE were tested in a univariate and multivariate analysis using logistic regression techniques. Finally a ROC analysis was undertaken to measure predictive accuracy and validate the model.

Results: The incidence of CRNE was 19.3%. Female gender, metastatic stage, treatment with platinum or anthracyclines-based chemotherapy, and low baseline hemoglobin or neutrophil count were independent predictive factors for CRNE. The accuracy of the model was 82.8% with sensitivity of 24.2%, specificity of 97.7%, positive and negative predictive values (PV) 71.4% and 84.3% respectively. The ROC analysis of training datasets yielded an area under the curve (AUC) of 0.791 (95%CI: 0.729 – 0.852). A ROC curve plotted for the validation yielded a similar AUC (0.836; 95%CI: 0.769-0.944), accuracy (85%), Sensitivity (47.4%), Specificity (96.3%), PV+ (75%) and PV- (86.6%).

Conclusions: This model can identify patients at high risk of CRNE before the chemotherapy with low or intermediate risk of FN is started, allowing clinicians an opportunity to plan appropriate and timely neutropenia management.

Clinical trial identification: The number of the trial protocol: AFI-QUI-2011-01
Legal entity responsible for the study: APIDIO. Asociación para el Fomento de la Investigación y Desarrollo Integral de la Oncología
Funding: AMGEN
Disclosure: All authors have declared no conflicts of interest.

Table: 1453P

<table>
<thead>
<tr>
<th>Total (%)</th>
<th>HEC (%)</th>
<th>AC/EC (%)</th>
<th>MEC (%)</th>
<th>LEC (%)</th>
<th>mEC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent</td>
<td>25.5</td>
<td>9.1</td>
<td>0</td>
<td>4</td>
<td>63.8</td>
</tr>
<tr>
<td>Inconsistent of which: Only acute - Only delayed</td>
<td>74.5</td>
<td>90.9</td>
<td>100.0</td>
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<td>93.6</td>
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<tr>
<td>acute and delayed</td>
<td>29.2</td>
<td>70.6</td>
<td>63.7</td>
<td>0</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Conclusions: Although the existence of specific AP guidelines, there is still a lack of adherence to evidence-based literature, both in the way of under- and over-prescription. This underscores the need of implementing education for healthcare professionals and usage of informatics tools for antiemetic therapies in everyday clinical practice to reduce inconsistencies and to increase adherence to guidelines.

Legal entity responsible for the study: Polo Oncológico, Azienda Ospedaliero-Universitaria Pisana
Funding: Polo Oncologico, Azienda Ospedaliero-Universitaria Pisana
Disclosure: All authors have declared no conflicts of interest.

Impact of sepsis and organ dysfunction on cancer patients’ mortality
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Background: Infection is a significant complication in cancer patients, which frequently prolongs hospitalization. Severe sepsis can also lead to acute organ dysfunction and eventually death. This study aimed to identify cancer patients with sepsis and organ dysfunction, and to assess its impact on mortality.

Methods: We reviewed medical data of cancer patients in a tertiary hospital, with diagnosis of sepsis, between January 2013 and April 2014. Descriptive analysis of main demographic, clinical and prognostic characteristics was performed. Identification of independent predictors of organ dysfunction and mortality was accomplished by binary logistic regression.

Results: We included 287 patients with a median age of 67 years, 58% were male and 80% had a solid tumor; 25% gastrointestinal (GI), 18% lung and 16% genitourinary (GU). Half of patients presented a respiratory focus of infection and organ dysfunction were reported in 35% of patients. There was a significant association between primary tumor location and focus of infection (p < 0.05). Respiratory infections were more frequent in lung cancer patients (27%), a urinary focus was present in 27% of GU and an abdominal focus in 53% of GI cancer patients. There was a significant association between organ dysfunction and primary tumor location, which was more frequently present in GI and lung cancer patients (25% and 19% respectively, p < 0.01). Global mortality was 25%. Patients with hyperlactacidemia presented a higher risk for organ dysfunction (2.44). Hyperlactacidemia (OR 3.206, p = 0.018), number of organ dysfunction (OR 5.738, p = 0.019) and MEDS score (OR 1.103, p = 0.021) were significant risk factors for mortality. Cancer patients with liver dysfunction presented the higher risk of death (OR 6.56, p = 0.008).

Conclusions: Severe sepsis is a common and deadly complication in cancer patients. Focus of infection was related to primary tumor location. Number of organ dysfunction, hyperlactacidemia and MEDS score were associated to an increased risk of mortality. Nevertheless, more studies are needed to estimate the magnitude of this problem, in order to improve medical management with positive impact for cancer survival.

Legal entity responsible for the study: IPO-Porto, Hospital de São João
Funding: IPO-Porto, Hospital de São João
Disclosure: All authors have declared no conflicts of interest.

The primary prophylaxis of pneumocystis pneumonia by low-dose trimethoprim-sulfamethoxazole during R-CHOP therapy
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Background: Pneumocystis pneumonia (PCP) is frequently observed in immunocompromised patients. Currently, oral administration of trimethoprim-sulfamethoxazole (TMP-SMX) at a dose of 1 tablet daily (7 tablets/week) or 2 tablets twice a day, twice a week (8 tablets/week) is considered as standard for prophylaxis. However, they sometimes induce unpleasant toxicities such as rash,
leukopenia and renal dysfunction. To avoid them, dose reduction of TMP-SMX could be considerable. Rituximab plus CHOP therapy (R-CHOP) is a standard treatment for B-cell lymphoma. Since rituximab is immunosuppressive, prophylaxis of PCP is widely introduced. In our institute, low-dose TMP-SMX has been employed in such situations. To assess the efficacy and tolerability of the regimen, retrospective analysis was performed.

Methods: We reviewed patients with newly diagnosed B-cell lymphoma who completed 6 to 8 cycles of R-CHOP in our institute. In all patients, low-dose TMP-SMX consisting of 1 tablet twice a day, twice a week (4 tablets/week) was started simultaneously with R-CHOP. To improve medication adherence, administration day was fixed on Tuesday and Friday.

Results: From January 2009 to September 2014, 292 patients with a median age of 67 (21-89) were treated. They included diffuse large B-cell lymphoma (n = 231), follicular lymphoma (n = 65), mantle cell lymphoma (n = 6) and others (n = 8). The median length of prophylaxis from the last day of R-CHOP was 5.7 (0.6-16.6) months. The median platelet count decreased from 1.1 (0.07-19.2) to 0.4 (0.03-1.4) x 10^12/L. During treatment. Of 292 patients, 291 showed no evidence of PCP. Although 1 patient developed PCP, the diagnosis was given on day 12 of the first cycle indicating that the patient was not on prophylaxis. In the other 291 patients, TMP-SMX was well tolerated and no related adverse event was observed.

Conclusions: Four tablets of TMP-SMX a week may be sufficient to prevent PCP during R-CHOP. In addition, minimum toxicities are expected by this method. As we demonstrated in our study, the elderly patients who need R-CHOP are increasing. In this context, our data provide a valuable insight into the total strategy of lymphoma treatment.

Legal entity responsible for the study: Chiba Cancer Center

Funding: Chiba Cancer Center

Disclosure: All authors have declared no conflicts of interest.

Underutilization of G-CSF in elderly cancer patients – an issue that needs to be urgently addressed

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Background: Chemotherapy-induced febrile neutropenia (FN) is a potentially life-threatening side-effect of chemotherapy. Prophylactic use of granulocyte colony stimulating factors (G-CSF) reduces the risk of FN. G-CSFs also appear to reduce cost and improve patients’ quality of life. The aim of our study was to assess the use of G-CSF among elderly cancer patients (≥70 years), i.e. in a group of patients with shortest survival rates.

Methods: We conducted a retrospective medical record review in tertiary hospital. A total of 176 chemotherapy order forms from January to February 2015 were analyzed. The use of G-CSF was compared to European Organization for Research and Treatment of Cancer and National Comprehensive Cancer Network guidelines.

Results: Out of 176 patients, 82 were male and 94 female. The patients were 70 to 93 years old (average 76.4). The most common diagnose among men was colorectal cancer (n = 31) and among women breast cancer (n = 36). Chemotherapy regimens with high risk of FN were prescribed to 13 (4.2%) and with intermediate risk to 11 (3.4%) patients. According to the guidelines, prophylactic use of G-CSF is indicated for all patients with high risk regimens and for selected patients (with additional risk factors, including age >65) with intermediate risk regimens. Our study revealed that none of the elderly patients in intermediate risk chemotherapy group received G-CSF. Moreover, most of these elderly patients had 1 or more additional risk factors (female gender, previous chemotherapy/radiation, previous neutropenia, recent surgery, poor performance status, poor renal and liver function), due to which the prophylactic use of G-CSF would have been indicated. Most importantly, we found that none of patients in high risk chemotherapy group received G-CSF which poses serious risk of developing FN leading to treatment failure.

Conclusions: Our study indicated a significant underutilization of G-CSF in elderly cancer patients, especially in those receiving regimens with high risk of FN. LIP was used in 2 cases due to FN. Nevertheless, our study revealed that none of patients in high risk chemotherapy group received G-CSF which poses serious risk of developing FN leading to treatment failure.

Legal entity responsible for the study: Tartu University Hospital

Funding: Tartu University Hospital

Disclosure: All authors have declared no conflicts of interest.

145/PF Prophylaxis of chemotherapy-induced neutropenia with lipogfilgrastim in patients with breast cancer: results from an interim analysis of the non-interventional study NADIR

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Background: Anthracycline and/or taxane-based (A/T) chemotherapy (CTx) are among the most effective treatments in breast cancer (BC). Many modern A/T regimens used in BC including dose-dense (dd) protocols with treatment intervals of ≤2 weeks are associated with a significant incidence of febrile neutropenia (FN) thus forcing a primary prophylaxis using granulocyte colony-stimulating factors (G-CSF). Lipogfilgrastim (LIP) is a glyco-pegylated G-CSF approved to reduce the duration of neutropenia and the incidence of FN. In 2014, a large-scale non-interventional study (NIS) was initiated to obtain detailed information on the value of LIP in order to prevent both FN and severe neutropenia. Here we report on results from an interim analysis of the NIS NADIR focusing on the subset of pts with BC.

Methods: The prospective multicenter NIS NADIR is conducted in 270 outpatient centers and hospitals across Germany aiming to collect data on prophylactic LIP use in 2500 pts with different tumor entities subjected to CTx in the clinical routine. The objective of the study is to assess the effectiveness of LIP by determining the incidence of neutropenia grade 3/4 and FN.

Results: At the time of data cut-off (3/2016), 2422 pts were enrolled by 198 sites. 1556 pts were evaluable; 741 pts were diagnosed with BC, of whom 274 were treated with dd regimens. Mean age was 54.6 ± 5.4 years for all BC pts and pts with dd regimens, respectively. In 89.9 ± 9.6% of pts, CTx was applied in an adjuvant setting. Overall 96.1% of pts were treated with regimens containing A/T. 94.6/ 96.1% of documented CTx cycles were supported by LIP. Neutropenia grade 3/4 occurred in 29.4 ± 35.9% of pts, 2.2/ 1.8% developed FN. Dose reductions were reported in 5.5/ 4.2% of cycles, in 0.7% 0.6% of cases due to CTx-induced neutropenia. For 26.7/ 34.3% of pts LIP-related adverse events (AE) were reported. The most frequent LIP-related AE was bone pain (11.1/ 18.6%). LIP-related serious adverse events were reported for 2.4/ 3.3% of pts.

Conclusions: LIP was effective and well tolerated in BC pts treated with A/T as well as in the subgroup of pts with dd regimen. The low incidence of neutropenia grade 3/4 and FN was comparable to previous publications.

Clinical trial identification: Study Protocol No. TV44689-ONC-4004

Legal entity responsible for the study: Ethikkommission der Landesärztekammer Baden-Württemberg

Funding: TEVA GmbH


145/SF Development of a prognostic system to predict the response to treatment of neutropenic fever

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Background: Febrile neutropenia (FN) remains one of the most commonly encountered oncologic emergencies in patients (pts) with hematological malignancies. Development of a prognostic system will help to improve the outcome in those pts.

Methods: This is a prospective observational study including 142 pts with haematological malignancies who presented to Kasr Al Ainy Center of Clinical Oncology during the period 1st of June 2014 to October 2015. This group of pts suffered from 276 episodes. According to the MASCC score, high risk pts were treated inpatients. All admitted pts were subjected to blood, sputum, stool and urine cultures withdrawal and Galactomann test. PCR (polymerase chain reaction) of sepsis and B&AL (bronocho-aveolus lavage ) were done in certain cases. Empirical antibiotics were started immediately, antifungal and antiviral treatments were reviewed according to the guidelines.

Results: The different diagnostic modalities were analysed in addition to the results of treatment by different classes of antibiotics. The most frequent diagnosis in our study were AML (35 pts), followed by ALL (27pts), NHL (35 pts).The disease status was found to be highly significant and affect the control of neutropenic fever episode. The more the patient developed neutropenic episodes the more the risk of mortality. In our
study, the MASCC score was highly significant. 62% of the identified pathogens were gram positive detected by blood culture, while gram negative bacteria were the commonest pathogens identified by other diagnostic modalities.

### Table: 1458P Multivariate analysis to determine pretreatment variables of independent prognostic value

<table>
<thead>
<tr>
<th>Variable</th>
<th>odds</th>
<th>95% CI</th>
<th>P-value</th>
<th>Weighted partial ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous FN episode</td>
<td>1.47</td>
<td>0.307 - 7.023</td>
<td>0.63</td>
<td>-</td>
</tr>
<tr>
<td>Disease burden</td>
<td>3.677</td>
<td>1.2 - 11.265</td>
<td>0.023</td>
<td>2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5.609</td>
<td>1.711 - 18.392</td>
<td>0.004</td>
<td>3</td>
</tr>
<tr>
<td>Previous fungal infection</td>
<td>1.905</td>
<td>0.407 - 8.91</td>
<td>0.413</td>
<td>-</td>
</tr>
<tr>
<td>Uncontrolled disease</td>
<td>4.222</td>
<td>1.019 - 17.493</td>
<td>0.047</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The sum of the weighted partial scores of the three significant variables resulted in a prognostic score ranging from 0 (best prognosis) to 7.5 (worst prognosis). Cut-off value of 4.5 was determined and it divides patients into two groups, ≤4.5 vs. >4.5.

### Conclusions:
Many risk factors affect the outcome of FN and should be taken into consideration for every pt.

### Legal entity responsible for the study: Hamdy Zawam

### Funding: Not applicable

### Disclosure: All authors have declared no conflicts of interest.

## Use of lipogefilgrastim in clinical practice for the prophylaxis of chemotherapy-induced neutropenia: interim results of pan-European non-interventional study

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### Background:
Lipogefilgrastim (Lonquex®) is a long-acting glycopegylated G-CSF that was proven to be non-inferior with regard to duration of severe neutropenia compared with pegfilgrastim in breast cancer patients. The objective of this study was to evaluate effectiveness of lipogefilgrastim in everyday clinical practice in adult patients with different tumor types who are treated with cytotoxic chemotherapy.

### Methods:
This is a prospective non-interventional study. Patients with different tumor types treated with cytotoxic chemotherapy (CT), who received lipogefilgrastim in primary (PP) or secondary prophylaxis (SP) are included in this study. CT dose modifications and neutropenia-related events are recorded and analyzed. Evaluation of effectiveness following the first lipogefilgrastim-supported treatment cycle is presented here.

### Results:
At the time of analysis (March 2016), a total of 621 patients were included. Majority of included patients was 59.2 ± 13.2 and 67.6% were female. Most patients had breast cancer (39.8%) and lymphoma (24.0%). Exposure to lipogefilgrastim has been documented for 507 patients. Data on CT dose modifications and neutropenia-related events following the first lipogefilgrastim-supported cycle were available for 409 and 444 patients, respectively. CT dose omissions were observed in 0.3% patients when lipogefilgrastim was applied in PP. No omissions were observed when it was applied in SP. CT dose delays were observed in 10.3% (PP) and 15.8% (SP) of patients and CT dose reductions in 5.2% (PP) and 7.5% (SP) of patients. Febrile neutropenia was recorded in 1.4% (PP) and 1.2% (SP) of patients, whereas severe neutropenia was recorded in 1.9% (PP) and 4.7% (SP) of patients. A total of 89 (17.8%) patients exposed to lipogefilgrastim reported at least one adverse drug reaction (ADR). The most common ADRs were myalgia, bone pain, and headache. Serious ADRs were reported by 25 (4.9%) patients.

### Conclusions:
Lipogefilgrastim is effective and well tolerated in the real world setting administered either in PP or SP. Both effectiveness and safety data obtained in this study, are in line with published data for lipogefilgrastim.

### Clinical trial identification: N/A

### Legal entity responsible for the study: Teva Pharmaceuticals

### Funding: Teva Pharmaceuticals

### Disclosure: E. Petru: Honoraria from Teva, Roche, Amgen, Sandor. All other authors have declared no conflicts of interest.

## A multi-centre study to investigate the natural history of taxane acute pain syndrome (TAPS) in patients receiving taxane-based chemotherapy for breast or prostate cancer

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### Background:
Taxane acute pain syndrome (TAPS) is characterized by myalgia and arthralgia starting 24-48 hours after taxane-based chemotherapy and lasting up to 7 days. Despite its negative impact on patient quality of life, its characteristics and natural history remain poorly defined. This study evaluates persistence, severity and the impact of TAPS on quality of life (QoL).

### Methods:
Eligible patients with breast or prostate cancers peri-monthly taxane-based chemotherapy completed the Functional Assessment of Cancer Therapy-Taxane (FACT-T), Brief Pain Inventory (BPI) questionnaires and a pain medication diary daily for 1 week after each chemotherapy infusion. TAPS was defined through myalgias and arthralgias on questionnaires.

### Results:
From March to December 2015, of 52 patients enrolled 409 completed the study. 66% of breast patients reported TAPS. TAPS started 24-72 (range 24-96) hours after treatment infusion reaching a peak by day 3 (range 1-5). TAPS was more common in the legs and back. Dose reductions, delays or treatment discontinuation were not required due to TAPS. Medications used to treat TAPS included opioids (n = 3) and NSAIDs (n = 9). There was negative effect of pain on QoL in pain scores at baseline in comparison with the final infusion cycle (mean change in “BPI worst pain” score was +1.61 and FACT-T score was −6.9, with p-values 0.014 and 0.017, respectively).

### Conclusions:
TAPS is a common toxicity and associated with a negative impact on QoL. Further data will help define predisposing risk factors. Prospective patient-reported outcome assessments are crucial to individualize treatment strategies and to improve management of TAPS.

### Clinical trial identification: NCT02363608

### Legal entity responsible for the study: Ottawa Hospital Regional Cancer Centre

### Funding: Ottawa Hospital Regional Cancer Centre (Internal)

### Disclosure: All authors have declared no conflicts of interest.

## Effect of solution pre-warming, hot compress, plus pH adjustment by combination with dexamethasone on venous pain in cancer patients receiving oxaliplatin via a peripheral vein

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### Background:
Central venous port-free administration of oxaliplatin in combination with an oral fluoropyrimidine improves patient satisfaction; however, pain provoked by peripheral intravenous administration of oxaliplatin may reduce compliance. There are recent reports that pH adjustment by combination with dexamethasone, pre-warming of the solution, or a hot compress over the peripheral catheterization site, reduces peripheral venous pain. To date, the therapeutic benefit of the combination of these interventions has not been established. The aim of this study was to clarify the efficacy of this combination for venous pain in cancer patients receiving oxaliplatin via a peripheral vein.

### Methods:
We treated all outpatients with the above combination after April 2012. The venous pain was defined as grade ≥2, according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
for Adverse Events version 4.0. We retrospectively reviewed the electronic medical records from cancer patients who had received oxaliplatin via a peripheral vein between December 2009 and June 2014. The study protocol was approved by the Ethics Committee of Ehime University Hospital (approval number: 160207).

Results: We evaluated 271 treatment courses in 59 patients. Venous pain occurred in 42 courses (15.5 %) among 26 patients. Multivariate logistic regression analysis revealed that female sex and body mass index ≥25 were significantly associated with an increased risk of venous pain during all courses (adjusted odds ratios [OR]: 3.18, 95 % confidence interval [CI]: 1.35–7.92, p = 0.008 and adjusted OR: 3.37, 95 % CI 1.27–9.40; p = 0.015, respectively). Combination of pre-warming the solution, use of a hot compress, plus pH adjustment combined with dexamethasone were significantly associated with a reduced risk of venous pain during all courses (adjusted OR: 0.11, 95 % CI 0.02–0.44; p = 0.002).

Conclusions: This is believed to be the first study to establish the analgesic effect of combination of pre-warming the solution, use of a hot compress, plus pH adjustment by combining with dexamethasone on venous pain in cancer patients receiving oxaliplatin through a peripheral vein.

Legal entity responsible for the study: Ehime University Hospital

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

1462P  Opiophobia – knowledge, attitudes and concerns about opioid medicines among Polish society, cancer patients, families and professionals – the first wave of a survey

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Background: Opiophobia is one of the major issues limiting cancer and chronic pain treatment in Poland. This study is the first stage of national survey addressing the issue of opioaphobia among professionals and others.

Methods: The study included a total of 1248 people, in that 141 doctors (age 24 to 84y; M = 44.29; SD = 13.28), 85 nurses (age 29 to 61y; M = 45.47; SD = 8.94), 167 cancer patients/pts (age 20 to 100y; M = 59.11; SD = 21.27), 131 members of pts families (age 16 to 99y; M = 52.15; SD = 19.85), 212 students (age from 18 to 36y; M = 24.55, SD = 5.41), and 402 others people (age 16 to 99y; M = 3.85;SD = 16.04), defined as a society. Internet or paper version of the questionnaires, which included 8 categories of questions for professionals, 4 for others, including: demographic, job experience with opioids, prescribed painkillers, knowledge about opioids, difficulties and concerns, etc.

Results: 65-89% of study participants had experienced cancer in their family, but only 50% identified relatives suffering chronic pain. Despite each Polish physician having the right to prescribe opioid medicines, just 1/3 of them were convinced they have no rights to do this, and 1/3 had never applied to the NIH for special prescriptions for opioids. Approximately 70% of pscyians and 30% of nurses felt qualified in opioid treatment. Fentanyl and buprenorphine patches, as well as morphine tablets were most opioids. Approximately 70% of physicians and 30% of nurses felt qualified in opioid treatment on lower level than in western EU, opioids addiction in Poland is a big problem, etc.

Conclusions: Opiophobia is still a big problem among professionals and nonprofessionals in Poland. However, doctors and nurses are qualified to use these medicines on a daily basis, but they limit prescriptions fearing restrictions from the NIH under pressure from family and patient expectations.

Legal entity responsible for the study: Mossakowski Medical Research Centre; Polish Academy of Sciences

Funding: Mossakowski Medical Research Centre; Polish Academy of Sciences

Disclosure: All authors have declared no conflicts of interest.

1463P  Denosumab for the prevention of symptomatic skeletal events (SSEs) in patients with bone-metastatic breast cancer: A comparison with skeletal-related events (SREs)


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Background: A randomised controlled phase 3 trial of patients with breast cancer and bone metastases demonstrated denosumab was superior to zoledronic acid in reducing bone complications (SREs, defined as pathological fracture, surgery or radiation to bone, or spinal cord compression) (Stopeck AT, et al. J Clin Oncol 2010;28:5132–39).

Recently, a composite endpoint of SSEs (symptomatic fracture, surgery or radiation to bone) or spinal cord compression had been introduced as an alternative measurement of clinically relevant skeletal morbidity.

Methods: Eligible patients had confirmed breast cancer, evidence of ≥1 bone metastasis and had received no prior intravenous (IV) bisphosphonates. Patients were randomised double-blind to subcutaneous (SC) denosumab 120mg/IV placebo or IV zoledronic acid 4mg (adjusted for creatinine clearance)/SC placebo every 4 weeks. Daily oral calcium and vitamin D supplements were recommended. This post-hoc SSE analysis of the patient population includes symptomatic pathologic fractures (per investigators’ judgement), spinal cord compressions and the requirement for preventative or corrective surgery or palliative radiation to bone.

Results: As previously reported, fewer patients who received denosumab than zoledronic acid had confirmed first and subsequent SREs (Table). Similarly, fewer patients who received denosumab versus zoledronic acid had confirmed first and subsequent symptomatic events (SSEs). The median (95% CI) estimate of time to first SSE for both denosumab and zoledronic acid was not reached (HR = 0.76 [0.61, 0.93] P < 0.001).

Table: 1463P

<table>
<thead>
<tr>
<th>Number of Confirmed Events</th>
<th>Denosumab (N = 1,020)</th>
<th>ZA (N = 1,020)</th>
<th>Hazard or Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First SSE, n (%)</td>
<td>156 (15.2)</td>
<td>198 (19.4)</td>
<td>HR = 0.76 (0.61, 0.93) P &lt; 0.01</td>
</tr>
<tr>
<td>First SSE, n (%)</td>
<td>315 (30.7)</td>
<td>372 (36.5)</td>
<td>HR = 0.82 (0.73, 0.95) P &lt; 0.01</td>
</tr>
<tr>
<td>First and subsequent SSEs</td>
<td>197</td>
<td>268</td>
<td>RR = 0.73 (0.59, 0.90) P &lt; 0.01</td>
</tr>
<tr>
<td>First and subsequent SSEs</td>
<td>474</td>
<td>608</td>
<td>RR = 0.87 (0.66, 0.98) P = 0.003 (Superiority)*</td>
</tr>
</tbody>
</table>

*Adjusted for multiplicity

Conclusions: Denosumab reduced the risk of skeletal events in patients with bone-metastatic breast cancer to a similar extent regardless of whether the endpoint was defined as SRE or SSE. The risk of developing first and subsequent SSEs was reduced by up to 27% when comparing denosumab with zoledronic acid.

Clinical trial identification: NCT00321464

Legal entity responsible for the study: Amgen

Funding: Amgen

Disclosure: J.J. Body: Lecture and consulting fees for Amgen. R. von Moos: Advisory Board: Amgen, Bayer, GSK, Novartis & Roche Research Grant: Bayer. M. Martin: Advisory Boardwork, Novartis & AMGEN; Research funding Novartis. G. Steger: Honoraria from Amgen; Travel support and honoraria from Novartis. H. de Boer: Received honorarium/speakers fees from Amgen Australia. H.-S. Radcliffe, D. Niepel: Employee of Amgen and holds Amgen stock. A.T. Stopeck: Received honorarium/consulting, Amgen; consulting: Pfizer, Sanofi, Biomarin, Peregrine. All other authors have declared no conflicts of interest.
**Methods:** This was a randomized, 3 period single dose crossover study in 36 healthy subjects aged 18-50 yr. Eligibility was assessed within 14 d of the first dose. IMP was administered in the fasted state on Day 1 of each treatment period. PK samples were collected up to 24 h (saliva) / 96 h (blood) for measurement of clonidine concentration. Safety and tolerability were evaluated at specified times throughout the study. A washout period of at least 7 d was observed between administrations.

**Results:** There were 15 and 13 adverse events (AEs) considered at least possibly related to IMP following 50 µg and 10 µg MBT, respectively, compared to 26 following 100 µg clonidine OT. All AEs were either mild or moderate in severity. No serious AEs were reported. Dry mouth and fatigue were reduced in clonidine MBT 50 µg and 100 µg compared to placebo in head and neck cancer patients undergoing chemoradiation. This study compared the pharmacokinetics (PK), safety, and tolerability of clonidine MBT with a reference oral tablet (OT).

**Conclusions:** Clonidine MBT is well tolerated and exhibits proportional saliva and plasma concentration and exposure data is presented below.

### Table: 1464P

<table>
<thead>
<tr>
<th></th>
<th>PLASMA</th>
<th>PLASMA</th>
<th>SALIVA</th>
<th>PLASMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 µg clonidine OT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>399 (86.1)</td>
<td>5640 (1290)</td>
<td>2630 (240)</td>
<td>14600 (8220)</td>
</tr>
<tr>
<td>Plasma AUC&lt;sub&gt;0-24&lt;/sub&gt; (h*pg/mL)</td>
<td>222 (59.3)</td>
<td>4700 (1220)</td>
<td>38700 (2090)</td>
<td>2920000 (146000)</td>
</tr>
<tr>
<td>100 µg clonidine MBT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>234 (26.9)</td>
<td>1660 (720)</td>
<td>20900 (132000)</td>
<td>890000 (1132000)</td>
</tr>
<tr>
<td>Plasma AUC&lt;sub&gt;0-24&lt;/sub&gt; (h*pg/mL)</td>
<td>148000 (173700)</td>
<td>2920000 (146000)</td>
<td>211 (26.5)</td>
<td>0.81 (0.66, 0.99)</td>
</tr>
<tr>
<td>50 µg clonidine MBT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>399 (86.1)</td>
<td>5640 (1290)</td>
<td>2630 (240)</td>
<td>14600 (8220)</td>
</tr>
<tr>
<td>Plasma AUC&lt;sub&gt;0-24&lt;/sub&gt; (h*pg/mL)</td>
<td>222 (59.3)</td>
<td>4700 (1220)</td>
<td>38700 (2090)</td>
<td>2920000 (146000)</td>
</tr>
</tbody>
</table>

### Table: 1465P

<table>
<thead>
<tr>
<th></th>
<th>Number of Confirmed Events</th>
<th>Denosumab (N = 800)</th>
<th>ZA (N = 797)</th>
<th>Hazard or Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First SSE, n (%)</td>
<td>181 (22.7)</td>
<td>211 (26.5)</td>
<td>HR = 0.81 (0.66, 0.99)</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>First SRE, n (%)</td>
<td>236 (29.5)</td>
<td>277 (34.8)</td>
<td>HR = 0.81 (0.68, 0.96)</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>First and subsequent SREs</td>
<td>234</td>
<td>264</td>
<td>RR = 0.86 (0.71, 1.04)</td>
<td>P = 0.11</td>
</tr>
<tr>
<td>First and subsequent SSEs</td>
<td>328</td>
<td>374</td>
<td>RR = 0.85 (0.72, 1.00)</td>
<td>P = 0.05</td>
</tr>
</tbody>
</table>

### Conclusions:
- Skeletal morbidity improved with denosumab versus zoledronic acid, regardless of whether the endpoint was defined as SRE or SSE. The risk of developing first and multiple SREs was reduced by up to 14% when comparing denosumab with zoledronic acid.
- Clinical trial identification: NCT00330759

Legal entity responsible for the study: Agena Funding: Agena Disclosure: R. von Moos: Advisory Boards: Agena, Bayer, GSK, Novartis, Roche, Research Grant: Bayer. G. Scagliotti: Consultant for Eli Lilly, Received honoraria from AstraZeneca, Roche, Pfizer, Eli Lilly and Clovis Oncology. V. Hirsh: Honoraria for Advisory Boards: Agena, Novartis, Roche, Pfizer, Astra Zeneca, Merck, Eli Lilly, BMS.

### Methodology:
- The study was a double-blind, randomized, placebo-controlled phase 3 trial in Japan. Cancer patients with OIC, defined as having opioid-induced constipation (OIC) as a side effect. Naldelemine (NAL), a peripherally-acting µ-opioid receptor antagonist (PAMORA), is being developed for the treatment of patients with OIC. The aim of this analysis was to assess the onset of action of NAL in the context of primary efficacy and safety results previously reported.
- **Methods:** The study was a double-blind, randomized, placebo-controlled phase 3 trial in Japan. Cancer patients with OIC, defined as having ≤ 5 spontaneous bowel movements (SBMs) during the 2-week qualification period, were evenly assigned to either oral NAL 0.2 mg QD or placebo (PBO). The primary efficacy endpoint was SBM responder rate (percentage of patients with ≥ 3 SBMs/week and an increase from baseline of ≥ 1 SBM/week) during the 2-week treatment period. To assess the onset of action, 1) time to the first SBM, 2) proportion of patients with at least 1 SBM at several
time points after initial dose and 3) change in frequency of SBMs/week from baseline to first week were evaluated.

**Results:** A total of 193 patients were randomized (NAL: 97, PBO: 96). The SBM responder rate of NAL was significantly larger than that of PBO (71.1% vs 34.4%, respectively; P < 0.0001). Besides, the time to onset of action of NAL was shorter than that of PBO with a shorter median time to the first SBM after the initial dose (NAL: 4.67, PBO: 26.58 hrs). The differences between the two groups in the proportion of patients with at least one SBM were statistically significant at all assessed time points (up to 4 hrs: 45.8% vs 73.3%, 8 hrs: 60.8% vs 14.6%, 12 hrs: 71.1% vs 25.0%, 24 hrs 77.3% vs 47.9%, P < 0.0001 for all). The change in the frequency of SBMs per week from baseline to the first week with NAL was significantly greater than with that with PBO (5.70 vs 1.73, P < 0.0001). The overall incidences of adverse events reported during the treatment period were 44.3% and 26.0% for NAL and PBO, respectively. Only diarrhea was reported for 2.5% of patients (19.6% vs 7.3%). However, the most cases were reported as mild and recovered.

**Conclusions:** Treatment with NAL led to timely improvement of OIC in patients with cancer and was generally well tolerated.

**Clinical trial identification:** JapCITI-132340, 15 November 2013

**Legal entity responsible for the study:** Shionogi & Co., Ltd.

**Funding:** Shionogi & Co., Ltd.

**Disclosure:** N. Katakami, Speakers Bureau Danpinpon Sumimoto, Chugai, Boehringer, AZ, Lilly, Taiho, Janssen, Novartis, Pfizer, Otsuka, Daiichi Sankyo Research Fund AZ, Eisai, Ono, Kyowa Hakko Kirin, Shionogi, Daiichi Sankyo, Taiho, Chugai, Lilly, Boehringer, Merck Serono, T. Harada: Honoraria Chugai Pharma, Taiho, Pharmaceutical, Ono Pharmaceutical, AstraZeneca KK, Novartis, Boehringer Ingelheim, K. Shinozaki: Honoraria Takeda, Merck Serono, KSR, AstZeneca, Novartis, Chugai, Daiichi Sankyo, Yoshida, Taiho, Kono, Otsuka, Yakult, T. Yokota, M. Arii, Y. Suzuki: Employee of Shionogi and have stock of Shionogi. N. Boku: Honoraria Taiho, Merck Serono, Ono, Shionogi, Chugai, Yakult, Daiichi Sankyo, Lilly, Takeda Research Funding Taiho, Chugai. All other authors have declared no conflicts of interest.

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### Table: 1467P

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Arm A (Control)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Arm B (Test)</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

**Neuropathy grade 0 1 Drop out**

<table>
<thead>
<tr>
<th>Grade</th>
<th>N (%)</th>
<th>1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (3.3%)</td>
<td>1 (3.3%)</td>
<td>18</td>
</tr>
<tr>
<td>2 (6.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

**TNF before start of treatment**

<table>
<thead>
<tr>
<th>mg/ml Mean ± SD Range</th>
<th>0.06</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03 ± 0.01 0.02 – 0.01</td>
<td>0.01 ± 0.02 0.02 – 0.06 0.06</td>
</tr>
<tr>
<td>0.01 ± 0.01 0.01 – 0.01</td>
<td>0.02 ± 0.01 0.01 – 0.04 0.0014</td>
</tr>
</tbody>
</table>

**TNF after 3 months of treatment**

<table>
<thead>
<tr>
<th>mg/ml Mean ± SD Range</th>
<th>0.044</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 ± 0.01 0.01 – 0.01</td>
<td>0.02 ± 0.01 0.01 – 0.04 0.0014</td>
</tr>
</tbody>
</table>

**Conclusions:** L-carnosine reduced the incidence of acute oxaliplatin induced neuropathy, delayed the onset of chronic neuropathy and decreased TNF α serum levels without additional toxicities. Further studies are warranted to examine the full potential of L-carnosine in chemotherapy induced neuropathy.

**Clinical trial identification:** Local registry: Cairo Univ 387658

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## Impact of hyponatremia in a tertiary cancer center: a one-year-survey at National Cancer Institute of Milan

**Funding:** 1. Ministry of Health, Labour and Welfare, Japan. 2. Japan Agency for Medical Research and Development (AMED)

**Disclosure:** Y. Eoe, J. Mizusawa, K. Takizawa, H. Katayama, K. Kataoka, M. Muto: Grants from Ministry of Health, Labour and Welfare, Japan, grants from Japan Agency for Medical Research and Development (AMED). K. Tobinai: Grants from Japan Agency for Medical Research and Development (AMED), during the conduct of the study; personal fees from Eisai, Takeda, Boehringer, Merck Serono. T. Harada: Honoraria Chugai Pharma, Taiho, Boehringer, Merck Serono. M. Arai, Y. Suzuki: Employee of Shionogi and have stock of Shionogi. N. Boku: Honoraria Taiho, Merck Serono, Ono, Shionogi, Chugai, Yakult, Daiichi Sankyo, Lilly, Takeda Research Funding Taiho, Chugai. All other authors have declared no conflicts of interest.

**Legal entity responsible for the study:** Japan Clinical Oncology Group (JCOG)

**Funding:** Japan Clinical Oncology Group (JCOG)

**Disclosure:** Y. Eoe, J. Mizusawa, K. Takizawa, H. Katayama, K. Kataoka, M. Muto: Grants from Ministry of Health, Labour and Welfare, Japan, grants from Japan Agency for Medical Research and Development (AMED). K. Tobinai: Grants from Japan Agency for Medical Research and Development (AMED), during the conduct of the study; personal fees from Eisai, Takeda, Mundipharma, Janssen, grants from Chugai, Kyowa Kirin, Ono, Cellgene, GSK, SERVIER, Abbvie, outside the submitted work.

**Background:** Hyponatremia (HN), defined as a serum sodium lower than 135 mmol/l, is the most common electrolyte disorder in hospitalized patients. Etiology is heterogeneous and a large difference exists in terms of symptoms and treatments. The aim of this study is to determine the incidence of HN in a Tertiary Cancer Center, evaluating possible influence in terms of prognosis and length of hospitalization.

**Methods:** This study includes all cancer patients hospitalized at our Institution from January 2015 to December 2015 for all causes other than HN. We analyzed retrospectively data regarding HN and correlation to age, sex, staging, histology. Survival distribution was estimated by Kaplan-Meier method, differences in probability of chi-square test.

**Results:** A total of 1,071 patients were included in the analysis. 243 (22.7%) presented at least one episode of HN; 197 (81.1%) showed mild hyponatremia (135-130 mmol/l), 44 (18.1%) moderate (130-125 mmol/l), 2 (0.8%) severe (< 125 mmol/l). Patients
were affected by lung cancer in 21.7%, breast cancer in 19.5%, colorectal cancer in 13.0% (others in 45.8%). Most patients had Stage IV disease (93.4%), male 44.7%, female 54.3%. Median age was 62.9 years. Concomitant diagnosis of SIADH was performed in 4 patients (8.8%). Resolution of HN after specific treatments was observed in 19 patients (41.3%), without significant differences about length of hospitalization between patients with normal and abnormal value at discharge. OS was lower in patients with moderate/severe HN versus mild (2.72 vs 6.81 months). Mortality rate was significantly lower in patients with corrected HN compared to not (52.6 vs 81.5%; p = 0.08), while no statistically significant difference was observed in OS (2.89 vs 2.63 months; p = 0.85).

Conclusions: HN represents a frequent occasional finding in hospitalized cancer patients, although in most cases it’s of mild degree. SIADH represents a small percentage of cases. In our experience HN is not associated to discharge delays. Independently by the underlying disease, moderate and severe HN identify a particular group of patients with poor prognosis, probably reflecting very advanced disease and palliative care needs.

Legal entity responsible for the study: Francesco Agustoni

Funding: Fondazione IRCCS Istituto Nazionale dei Tumori

Disclosure: All authors have declared no conflicts of interest.

1470P

Estimation of glomerular filtration rate in patients with abnormal body composition and relation with carboplatin toxicity

Department of Medical Oncology, Cochin Hospital, Paris Descartes University, APHP, CARPEM, CERTIM, Hôpital Cochin, Paris, France

Background: Carboplatin clearance is correlated with Glomerular Filtration Rate (GFR), which is usually evaluated with creatinine clearance using Cockcroft-Gault (CG) formula. Because serum creatinine (cCr) level is related to total muscle mass, we hypothesized that an abnormal body composition with a low lean body mass (LBM) percentage (LBM / weight) may result in GFR overestimation and inadequate carboplatin dose calculation by using CG formula. Serum cystatin C (cCy) is an alternative marker of GFR which is not affected by muscle mass. We aimed to correlate GFR creatinine (cCrGFR) and cystatin C (cCyGFR) to LBM percentage and the risk of toxicity. A high cCrGFR/cCyGFR ratio might estimate the miscalculation of GFR with cCr.

Methods: cCr and cCy were prospectively measured in consecutive cancer patients (pts) before chemotherapy. GFRc and GFRCy were calculated with CG and GRUBB formula, respectively. The LBM was assessed using CT-scan. Fibrile neutropenia and grade 3-4 thrombocytopenia were analysed in a subgroup of pts treated with carboplatin AUC 5 +/- paclitaxel.

Results: In 134 cancer pts (males 51%), median age was 63.7 (20–89). In 128 pts without severe renal insufficiency, cCr was correlated with LBM (r = 0.30, Pearson correlation coefficient, p < 0.005) but cCy was not correlated with LBM but significantly decreased in pts with the lowest LBM percentage. In this group of pts, the GFRc was significantly higher than GFRcy, indicating an over estimation of GFR with cCr (p = 0.039, Wilcoxon test). In 24 pts treated with carboplatin AUC 5 +/- paclitaxel, 6 pts had febrile neutropenia or grade 3-4 thrombocytopenia. Mean LBM percentage was lower in pts with limiting toxicities (49% vs 64%, p = 0.0002). Similarly mean GFRc/GFRcy ratio was higher in pts with limiting toxicities (1.9 vs 1.1, p = 0.004). By ROC analysis, the GFRc/GFRcy ratio value with the best sensitivity-specificity was 1.4. In the whole cohort, 43 pts (32%) have a GFRC/GFRCy ratio > 1.4.

Conclusions: Pts with a low LBM percentage (sarcopenic overweight pts) are at high risk of inadequate calculation of renal function, over dosage of carboplatin and increased acute limiting toxicity. High GFRC/GFRCy ratio allows to identify these pts. Legal entity responsible for the study: J. Alexandre

Funding: Fondation Martine Mudy

Disclosure: All authors have declared no conflicts of interest.

1472P

Chemotherapy in cancer patients undergoing hemodialysis: A multicenter study


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Background: Cancer is a major cause of death among patients undergoing hemodialysis (HD). However, little is known about the actual clinical practice of chemotherapy in cancer patients undergoing HD. Therefore, we conducted a nationwide questionnaire survey on chemotherapy for HD patients with cancer. Methods: This retrospective study included patients undergoing HD who were subsequently diagnosed with cancer from January 2010 to December 2012. We reviewed the clinical courses of the patients who underwent chemotherapy. The questionnaires that were sent to 20 institutions, members of the Onconephrology Consortium, consisted of the following sections: (1) patient characteristics; (2) regimen, dosing, and timing of chemotherapy; and (3) outcome.

Results: Overall, 675 patients were registered and the most frequent primary cancer sites were kidney, colorectum, stomach, lung, bladder, liver, breast, and pancreas. Of these patients, 74 received chemotherapy (44 as palliative chemotherapy, 30 as perioperative chemotherapy). The primary causes of renal failure were chronic glomerulonephritis (23 patients) and diabetic nephropathy (17 patients). The most commonly used cytotoxic drugs were fluoropyrimidine (15 patients) and platinum (eight patients), and the dosing and timing of these drugs differed between institutions; however, the dosing of molecular targeting drugs (24 patients) and hormone therapy drugs (15 patients) was consistent. The median survival time of patients undergoing palliative chemotherapy was 13.0 months (0.1 - 60.3 months). Of these, three patients (6.8%) died from treatment-related causes and eight patients (18%) died of causes other than cancer. A high proportion of the patients who had diabetic nephropathy died of causes other than cancer including two treatment-related causes. Of 30 patients who received perioperative chemotherapy, six (20%) died of causes other than cancer within three years after the initiation of chemotherapy.

Conclusions: Among HD patients with cancer who received chemotherapy, the rates of mortality from causes other than cancer might be high for both palliative and perioperative chemotherapy. The indications for chemotherapy in HD patients, particularly those with diabetes, should be carefully considered.
The effect of rikkunshito, a traditional Japanese herbal medicine, on food intake and plasma acylated ghrelin levels in lung cancer patients treated with platinum-based chemotherapy

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1Surgical Oncology, Hiroshima University, Hiroshima, Japan, 2Environmetrics and Biometrics, Hiroshima University, Hiroshima, Japan

Background: Platinum-based agents are key chemotherapeutic drugs for lung cancer patients. Although considerable progress has been made in supportive therapy for chemotherapy-induced nausea and vomiting (CINV), its preventive effect for delayed-onset CINV has not been always satisfactory. We aimed to evaluate whether rikkunshito (RKT), a traditional herbal medicine of Japan, improves CINV-induced anorexia and increases plasma acylated ghrelin (AG) levels, an orexigenic gut hormone known to alleviate CINV, in lung cancer patients receiving chemotherapy.

Methods: From July 2013 to March 2016, 40 lung cancer patients undergoing chemotherapy were enrolled and randomized to group A (1st course with RKT (7.5 g/day on days 1-14), 2nd course without RKT (control) or group B (1st course without RKT (control), 2nd course with RKT) in a prospective crossover study. All patients were administered cisplatin on day 1 and treated with 3HTx and NKJ receptor antagonists and steroids throughout the study. Mean food intake during 1st and 2nd courses from days 3 to 5 were compared with baseline food intake (day 1). Fasting blood samples were obtained on days 1, 3 and 5, and plasma AG levels (fmol/mL) were measured by enzyme-linked immunosorbent assay methods. The primary endpoint was food intake and secondary endpoint was plasma AG levels.

Results: Thirty-nine patients (male/female, 35/4; median age, 67 years) were included in the analysis. A decreasing rate of the food intake in the control course was significantly higher than that in the RKT course (control, 25%; RKT, 18%; p = 0.025). A significant drop in plasma AG levels from day 1 to day 3 was initially noted (RKT, 11.9, 7.3, p < 0.001; control, 13.3, 7.7, p < 0.001), followed by a marked increase from days 3 to 5 in the RKT course (7.3, 8.3, respectively, p = 0.020), but not in the control course (8.8, 7.7, respectively, p = 0.13).

Conclusions: RKT administration improves delayed-onset CINV-induced anorexia and increases plasma AG levels in lung cancer patients undergoing highly emetogenic chemotherapy.

Clinical trial identification: UMIN000010748

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Hydroactive colloid gel vs historical controls for the prevention of radiotherapy-induced moist desquamation in breast cancer patients: preliminary results

S. Censabeta1, S. Claes2, M. Otandri2, F. Baselines2, P. Bulens3
1Division of Medical Oncology, Jessa Hospital, Hasselt, Belgium, 2Limburn Oncology Center, Jessa Hospital, Hasselt, Belgium, 3CENSTAT, Interuniversity Institute for Biostatistics and Statistical Bioinformatics, Hasselt, Belgium

Background: Radiotherapy-induced moist desquamation (RIMD) is a painful side effect that might jeopardize radiotherapy outcomes. Previously, we found that the curative use of a hydroactive colloid gel, compared with dexpanthenol, significantly reduced the incidence of RIMD. In the present study, we investigated the efficacy of this same hydrogel in the prevention of RIMD.

Methods: Breast cancer patients scheduled for radiotherapy post-lumpectomy applied the hydroactive colloid gel from start to end of radiotherapy (Preventive Hydrogel group). They were compared with two groups of matched historical controls. One group applied a dexpanthenol cream throughout radiotherapy, the other replaced dexpanthenol with the hydrogel from day 11-14 of therapy (Curative Hydrogel group). Eligibility and radiotherapy fractionation (25Gy Gray [Gy] followed by a 8Gy boost) regimen were the same for the three groups. The incidence of RIMD was analysed through two-sample proportion tests (two-tailed) and logistic regressions.

Results: Overall, the incidence of RIMD was the lowest in the Preventive Hydrogel group (see Table 1). Although the difference with the Curative Hydrogel group did not reach significance when taking breast size into account, logistic regressions confirmed that patients in the Preventive Hydrogel group were at lowest risk of developing RIMD, irrespective of breast size (chi-square = 36.29, p < 0.0001; odds ratios = 0.18 for the Dexpanthenol group and 3.99, p = 0.0846; odds ratios = 0.54 for the Curative Hydrogel group).

Discussion: All authors have declared no conflicts of interest.

Table: 1474P Incidence of radiotherapy-induced moist desquamation (RIMD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Fraction 20 of RT</th>
<th>End of RT p*</th>
<th>Fraction 20 of RT</th>
<th>End of RT p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n = 25)</td>
<td>0.006</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>LT group (n = 30)</td>
<td></td>
<td>N (%)</td>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>RTOG grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1/1 (4)</td>
<td>3/10 (30)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>26 (96)</td>
<td>19 (70)</td>
<td>25 (83)</td>
<td>28 (93)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>7 (26)</td>
<td>2 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>3 (12)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Chi-square test or Fisher’s exact test (two-tailed).

Conclusions: In the control group the skin reactions developed into more severe forms (e.g. moist desquamation) towards the end of RT, whereas in the LT group the skin reactions remained stable. Results of this study show that PBMT is able to prevent aggravation of acute skin reactions of breast cancer patients undergoing RT.

Clinical trial identification: NCT02443493

Legal entity responsible for the study: Hasselt University

Funding: Hasselt University, Limburg Sterk Merkel, Province of Limburg, Jessa Hospital, Flemish Government, Limburgs Kankerfonds, ASA erf

Disclosure: All authors have declared no conflicts of interest.

Table: 1475P Photobiomodulation for the prevention of radiodermatitis: Preliminary results of a randomized controlled clinical trial in breast cancer patients

J. Robijns1, S. Censabeta1, S. Claes2, L. Buusel3, N. Helings1, I. Lambrecht1, A. Timmermans2, A. Maes3, P. Bulens1, V. Somers1, J. Melis2
1Faculty of Medicine & Life Sciences, Hasselt University, Hasselt, Belgium, 2Division of Medical Oncology, Jessa Hospital, Hasselt, Belgium, 3Division of Dermatology, Jessa Hospital, Hasselt, Belgium

Background: The aim of our study was to investigate the efficacy of photobiomodulation therapy (PBMT) for the prevention of radio dermatitis (RD) in breast cancer patients.

Methods: This is a randomized controlled, patient-blinded study with breast cancer patients that underwent an identical radiotherapy (RT) regime post-lumpectomy. A total of 57 patients were enrolled and randomly assigned to the intervention group to receive laser therapy (LT, n = 30) or the control group to receive a sham treatment (n = 27). LT was applied two days a week, immediately after the RT session, starting at the first day of RT. LT was delivered using a class IV ML5 laser that combines two synchronized laser diodes in the infrared range (808-905 nm) with a fixed energy density (4 J/cm2). There were no significant differences between the two groups with respect to patient- and treatment-related characteristics. The skin reactions were evaluated by trained, blinded nurses at fraction 20 and at the end of RT (fraction 33) according to the criteria of the Radiation Therapy Oncology Group (RTOG).

Results: At fraction 20 of RT the distribution of the RTOG grades was comparable between both groups (p = .238), with most of the patients presenting RTOG grade 1. At the end of RT, the severity of RD significantly differed between the two groups (p = .035), with a greater proportion of patients experiencing RD grade 2 or higher in the control group (30% vs. 7%, for the control and LT group, resp.). The skin reactions of the patients in the control group aggravated (p = .006), while they remained stable in the LT group (p = .205).

Table: 1475P Photobiomodulation for the prevention of radiodermatitis: Preliminary results of a randomized controlled clinical trial in breast cancer patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Fraction 20 of RT</th>
<th>End of RT p*</th>
<th>Fraction 20 of RT</th>
<th>End of RT p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n = 27)</td>
<td></td>
<td>N (%)</td>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>LT group (n = 30)</td>
<td></td>
<td>N (%)</td>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>RTOG grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Chi-square test or Fisher’s exact test (two-tailed).

Conclusions: These findings confirm and extend previous results: Applying the photoactive colloid gel from the start of breast cancer radiotherapy, rather than after fraction 11-14 or than dexpanthenol, significantly reduces the risk of developing RIMD.

Legal entity responsible for the study: Jessa Hospital

Funding: Jessa Hospital, Hasselt

Disclosure: All authors have declared no conflicts of interest.
Comparison of the usage of granulocyte colony-stimulating factors (G-CSF) in the Baltic and Nordic countries in 2011-2014

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Background: We aimed to analyse the use of G-CSF in the Nordic and Baltic countries and to compare the use of short- (filgrastim and its analogs) and long-acting (pegfilgrastim) G-CSFs in three cancer centres in Estonia with similar patient profile and identical reimbursement system.

Methods: G-CSFs were classified according to the Anatomical Therapeutic Chemical (ATC) classification (2015), the number of defined daily doses (DDD)/per 1000 inhabitants per day was used as a measurement (DDD is 350 mcg for filgrastim and 300 mcg for pegfilgrastim). National consumption data (based on wholesale data) of G-CSF in the Nordic and Baltic countries were obtained from the Estonian Agency of Medicines. Dispensed G-CSF in three cancer centres in Estonia was obtained from hospital pharmacies. Number of patients and chemotherapy courses delivered per year per hospital were retrieved from the Estonian Health Insurance Fund and were compared with the dispensed G-CSF in each country.

Results:

Table: The use of G-CSF in the Nordic and Baltic countries in 2011-2014 using DDD/1000 inhabitants/day

<table>
<thead>
<tr>
<th>Year</th>
<th>Finland</th>
<th>Norway</th>
<th>Sweden</th>
<th>Denmark</th>
<th>Lithuania</th>
<th>Latvia</th>
<th>Estonia</th>
<th>EE-1</th>
<th>EE-2</th>
<th>EE-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>0.7</td>
<td>0.1</td>
<td>0.04</td>
<td>0.1</td>
<td>0.04</td>
<td>0.07</td>
<td>0.03</td>
<td>0.37</td>
<td>0.67</td>
<td>0.12</td>
</tr>
<tr>
<td>2014</td>
<td>0.16</td>
<td>0.12</td>
<td>0.05</td>
<td>0.1</td>
<td>0.06</td>
<td>0.08</td>
<td>0.04</td>
<td>0.43</td>
<td>0.77</td>
<td>0.10</td>
</tr>
<tr>
<td>2015</td>
<td>0.14</td>
<td>0.11</td>
<td>0.05</td>
<td>0.2</td>
<td>0.07</td>
<td>0.1</td>
<td>0.05</td>
<td>0.57</td>
<td>1.0</td>
<td>0.13</td>
</tr>
<tr>
<td>2016</td>
<td>0.14</td>
<td>0.14</td>
<td>0.05</td>
<td>0.08</td>
<td>0.06</td>
<td>0.08</td>
<td>0.04</td>
<td>0.64</td>
<td>1.0</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Dispensed G-CSF (0.3mg) per chemotherapy courses in three cancer centres in Estonia. In 2014 the consumption of G-CSF in Sweden was 85% lower than in Denmark. Denmark and Finland using only pegfilgrastim. Latvia has used the most G-CSF when compared to other Baltics and in 2013 their use of long-acting G-CSF was 8 times higher than in Lithuania. Filgrastim was the most used G-CSF in Estonia, G-CSF consumption varied 5 fold between cancer centres.

Conclusions: According to the national medicines use data the overall consumption of G-CSFs is highly variable in the Nordic and Baltic countries despite clear and updated guidelines by ESMO and ASCO. Consumption of G-CSFs has steadily increased in the three Baltic countries, most likely due to the availability of filgrastim biosimilars. The observed remarkable differences between use of G-CSF in the Nordic countries are difficult to explain.

Legal entity responsible for the study: North Estonia Medical Centre, Tallinn, Estonia

Funding: All authors have declared no conflicts of interest.

Risk factors for upper limb deep venous thrombosis (DVT) associated with peripherally inserted central catheters (PICCs) in cancer patients

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Background: Peripherally inserted central catheters (PICCs) are associated with an increased risk of upper limb deep vein thrombosis (DVT). In Oxford University Hospitals, PICCs are widely used for the delivery of chemotherapy in cancer patients. We aimed to investigate the incidence and risk factors for PICC-associated DVT in cancer patients.

Methods: This was a single centre study at a tertiary centre in Oxford. We obtained details of all patients who had PICCs inserted in 2015 under the vascular access department in the hospital. Gender, Body Mass Index (BMI), cancer type and chemotherapy regime were matched to these patients. A diagnosis of upper limb DVT was confirmed from diagnostic imaging. Retrospective analysis on the data was performed.

Results: 454 oncology patients had PICCs inserted in 2015. 18 patients (4%) developed a DVT. Gender proportions were similar between the DVT and non-DVT cohorts (72% female vs 73% female, p = 0.89). Median BMI was 27.48g in those with DVTs and 26.84 in those without DVTs (p = 0.65). Breast cancer and colorectal cancer were the most common cancer types in the DVT cohort and breast cancer was over-represented whilst colorectal cancer under-represented compared to the non-DVT cohort (Table 1) (p = 0.59). A higher proportion of patients with DVTs received FEC-T chemotherapy compared to patients without DVTs (39% vs 25%, p = 0.20).

Conclusions: Other studies have extensively analysed risk factors for PICC thrombosis but have not focused on types of cancer or chemotherapy. In our study, breast cancer and FEC-T chemotherapy appeared to be over-represented in the DVT cohort, however this did not reach statistical significance. We are currently performing further work using data from previous years to see if this trend continues.

Legal entity responsible for the study: Oxford University Hospitals

Funding: Oxford University Hospitals

Disclosure: All authors have declared no conflicts of interest.

Predictive factors for use of parenteral versus oral anticoagulants in the treatment of venous thromboembolism in patients with active cancer

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Background: In patients with active cancer, the risk of venous thromboembolism (VTE) is up to five times higher. Anticoagulants (ACs) reduce the risk of VTE. We...
explored predictors for parenteral versus oral ACs in patients with cancer-associated VTE (Ca-VTE).

Methods: Patient data were retrieved from general practices in England contributing to the Clinical Practice Research Datalink (CPRD) with additional hospital discharge and cause of death data. The study cohort consisted of patients with a specified cancer recorded within the 90 days before or after the first VTE between 2008 and 2014, and with a subsequent record of either LMWH or fondaparinux defined as parenteral ACs (PACs) or K antagonists (VKA) or non-VKA oral ACs (NOACs). To allow for transition from PACs to VKAs, PAC only treatment was defined as initial PAC treatment without any VKA within the first 15 days. In a case-control analysis, cases were VKA users and controls only users, matched 1:1 on the date of the Ca-VTE. Adjusted incidence rate ratios were estimated from the odds ratios (ORs) using conditional logistic regression for matched case–control data. Adjustment included age, gender, tumour type, cancer therapy, lifestyle factors and comorbidities.

Results: The study cohort consisted of 5419 patients with a Ca-VTE. Of these, 34.5% were given PACs (mean age 66.5), 22.7% VKAs (mean age 70.2), 0.6% NOACs (mean age 67.6), and 42.1% received no ACs. A total of 1228 PAC users were matched to 1228 VKA users. With prostate cancer as the reference group, all other types of cancer were associated with preferential use of PACs. Pancreatic cancer (OR 7.69, 3.85–14.3), stomach cancer (OR 7.14, 3.70–14.3) and ovarian cancer (OR 6.67, 3.57–12.5) were the strongest predictors for initiation of PAC only therapy. History of diabetes (OR 1.37, 1.03–1.81) also predicted preferential PAC use. Predictors for preferential use of VKAs were age ≥80 compared with age 60–69 (OR 1.48, 1.08–2.03) and radiation therapy compared with chemotherapy (OR 1.63, 1.02–2.60).

Conclusions: Treatment with only PACs depends on the primary tumour and is more likely in patients with a history of diabetes. However, advanced age, and radiation therapy are predictors of VKA use.

Legal entity responsible for the study: Institute for Epidemiology, Statistics and Informatics GmbH

Funding: Bayer Pharma AG

Disclosure: A. Katholi: Grants from Bayer Pharma AG and grants from BMS/Pfizer outside the submitted work. K. Folkerts, M. Bach: Employee of the sponsor of this study. C. Martinez: Personal fees from Boehringer Ingelheim, grants from CSL Behring, grants from Bayer Pharma AG, grants from BMS-Pfizer, outside the submitted work.

A risk assessment model for predicting venous thromboembolic events in chemotherapy-treated germ-cell cancer

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Conclusions: We report a risk assessment model able to predict the probability of VTE in chemotherapy-treated GCC. This model may guide patient selection in studies of thromboprophylaxis in this population.

Legal entity responsible for the study: Spanish Germ Cell Cancer Group

Funding: Spanish Germ Cell Cancer Group

Disclosure: All authors have declared no conflicts of interest.

Outpatient management of cancer-associated pulmonary embolism (PE): analysis of lung carcinoma (LC) cohort from the Epiphany study


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Background: Clinical guidelines suggest that outpatient management of PE is an appropriate alternative in low-risk selected patients. However, this population is not adequately defined and the evidence is limited in cancer patients. Primary endpoint was the rate of success in outpatient PE management. Secondary endpoints included the analysis of complications and causes of readmission and mortality, re-thrombosis and major bleeding at 15, 30 and 90 days.

Methods: Epiphany is a Spanish multicenter ambispective and non-interventional study. It includes patients with cancer-associated PE, symptomatic and incidentally diagnosed, between October 2008 and October 2014. Patients were treated according to current international guidelines, and followed for at least 90 days. We present data from the LC cohort.

Results: We included 1033 patients with cancer and PE of whom 797 were diagnosed as outpatient. Of these, 210 had LC and 72 (34.3%) were discharged in the first 24-hours. 95.8% were incidental diagnoses and 83.3% did not show specific symptoms. The following features were associated with the last group (p <0.001): absence of symptoms due to PE or cancer, absence of hemodynamic instability and incidental diagnosis. Management was successful in 95.8% of cases. Major bleeding was the most frequent complication (14%). Presence of symptoms was the most common cause of readmission (50%). Need for oxygen therapy (49.3%) and respiratory failure (39.9%) followed in frequency. Overall 15, 30 and 90-day mortality was 1.4%, 4.2% and 13.9%, respectively. One patient (1.4%) had a major bleeding and no patient had re-thrombosis within the first 30 days. No significant differences between groups in terms of re-thrombosis or major bleeding were seen.

Conclusions: Within the limitations of an ambispective series and a subgroup analyses, this study suggest that most patients with LC and PE can be managed as outpatients, especially those with incidental PE. Additional studies are needed to better define the subgroup of patients at low risk of complications.

Legal entity responsible for the study: Virgen del Rocío University hospital

Funding: IBIS

Disclosure: All authors have declared no conflicts of interest.
Concerns of young women with breast cancer and their partners from chemotherapy to follow-up: a cross-sectional study
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Background: Better understanding the concerns of couples facing cancer appears crucial for care quality. This study aims to clarify the subjective experience in couples in which the woman is diagnosed with early breast cancer at a young age (< 45 years), by comparing patients and partners from chemotherapy to follow-up, and identifying differences and similarities in each course of treatment: chemotherapy, trastuzumab, hormone therapy and follow-up.

Methods: 491 couples (28.7% of which non-metastatic breast cancer women were under chemotherapy, 10.2% under trastuzumab, 33.9% under hormone therapy and 28.1% under follow-up) completed a self-administered questionnaire for patient: YW-BCL16 and for partner: corresponding version: partner YW-BCL16 (Christophe and al. Health Qual Life Outcomes 2015)), scale to identify respective subjective experience of disease (36 items, 8 dimensions).

Results: Patients reported more difficulties than partners in the management of child (ren) and the everyday life, body image and sexuality, negative affectivity and apprehension about the future, career management, and finances. Although the difficulties were generally more marked during chemotherapy and Trastuzumab than during hormone therapy and follow-up, the negative affectivity and apprehension about the future was high in every stage of treatment, especially in patients. The partners reported more difficulties in sharing with their close relatives, these difficulties increasing over time and also in patients. No difference appeared between patients and partners in the couple cohesion and deterioration of relationships with relatives.

Conclusions: Couples’ difficulties are particularly severe in the early care pathway and decrease over time, reflecting a progressive adjustment. A longitudinal study will substantiate this finding and allow to better identify some explanatory processes of these differences and similarities in the daily experience of the disease in couples.

Legal entity responsible for the study: Centre Oscar Lambret

Funding: This paper presents independent research funded by the Ligue Nationale contre Le Cancer, the Conseil Régional du Nord-Pas de Calais, the Prix Ruban Rose 2010, and Sanofi, Roche and Novartis

Disclosure: All authors have declared no conflicts of interest.

Supportive and palliative nutritional care for cancer patients (physicians and malnutrition and cachexia – a survey of healthcare providers (HCPs)

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Background: Malnutrition and cachexia are common in cancer pts and can negatively affect anti-cancer treatment response, toxicities and complications, survival and quality of life (QOL). Nutrition support can be effective in improving weight loss and, available practice guidance, as a prior survey (ESMO 2015, Abstr 1606) also reported. We hypothesize that the role of nutrition in supportive care and competencies managing cachexia are also contributors.

Methods: ECCO-ESMO-ECC 2015 delegates visiting the Nutricia booth took part in the survey, which was created by the authors.

Results: Of 963 participants, 72% were medical oncologists and 56% Europe based, mirroring congress attendee distribution. 44% routinely assess malnutrition before initiating, 38% during, and 9% after (curative) anticancer treatment. Importance of supportive nutrition was ascribed to curative (80%), noncurative (58%), and end-of-life care (39%). Main impacts of malnutrition were pt QOL (56%) or function (44%) and toxicities (53%), with high variation amid professions. Dietary advice and/or nutritional supplements were given > to 61% pts by 15%, and 21–60% by 56%, with the main goals QOL (69%), anticancer treatment completion (52%), and fast recovery (50%). Main nutritional care barriers were lack of assessment/monitoring tools (61%), costs of supplements (42%), no clear guidelines (29%), and lack of time (28%). Approaches to minimize weight loss were anesthetic therapy (56%), appetite stimulation (48%), and other anticachexia drugs (43%), more effective anticancer treatment (47%), and lowering the anticancer treatment dose (11%). 78% apply nutritional measures for cancer cachexia pts, but 9% were unaware of the cancer cachexia concept.

Conclusions: A small majority of HCPs recognize the negative impact of malnutrition and cachexia on cancer care outcomes, but a minority routinely apply nutritional assessment and care. Clinical practice tools, education, and guidelines are needed to improve nutritional care practice in cancer supportive and palliative care.

Legal entity responsible for the study: Nutricia

Funding: Nutricia

Disclosure: F. Strasser: Advisory board: Acaia, ACRAF, Amgen, Baxter, Celgene, Danone, Fresenius, GlaxoSmithKline, Grünenthal, Helmsln, Isis, Global, Millennium/Takeda, Mundipharma, Novartis, Novopharm, Nycomed, Otsuka, Pfizer, Pﬁzer-Olam; Part-time, PrIME, Santhera, Sunstone, Teva, Vifor.

Corporate-sponsored research: Novartis. Industry grants for clinical research: Celgene, Fresenius, Helmsln. R. Audisio: Corporate-sponsored research: Honoraria for independent presentations at meetings sponsored by industry (Nutricia and Roche).

N. Georgiou: Corporate-sponsored research Employee of Nutricia Advanced Medical Nutrition. All other authors have declared no conﬂicts of interest.

Vaccination perception and attitudes among patients with cancer receiving chemotherapy

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Background: Immunization against vaccine preventable diseases is an essential but mostly overlooked issue in oncology practice. Despite the presence of several guidelines, vaccination coverage rates among cancer patients are quiet low. We aimed to investigate the utilization of adult immunization recommendations and the perception of the patients with cancer receiving chemotherapy on immunization.

Methods: A 15-item questionnaire about immunization in adults with cancer diagnosed in adults with cancer was administered to patients with various cancers treated in daycare chemotherapy unit of Hacettepe University Cancer Institute.

Results: Total of 229 patients completed the survey. 74.7% of the patients agreed that people over 18 years of age must be vaccinated, and 54% of patients were vaccinated at least once, most commonly against influenza (25.3%) and tetanus (22.3%) over 18 years old. Higher rate of participants was opposed to vaccination of patients with cancer diagnosis compared with those who was opposed to vaccination of healthy adults (p < 0.001). The most frequent reason was the concerns of being harmful (40%). Vaccination was never recommended in 93% of the participants. Only 9% of patients (n = 21) were shot after cancer diagnosis, most commonly with influenza. There was a strong association between doctor’s advice and vaccination status. Twelve of 15 patients (80%) who were recommended to be vaccinated did so whereas only 9 of 214 remaining patients (4.2%) were vaccinated (p < 0.001). Among those not vaccinated after diagnosis of cancer, most frequent reason was; not recommended by the doctor (59%). Neither vaccination rates nor perceptions on adult immunization differed by age, gender, marital status, presence of co-morbidity or type of cancer. Interestingly, patients who had higher educational status had higher rate of opposition to vaccination after the diagnosis of cancer compared with those with lower educational status (p = 0.03).

Conclusions: Among adult patients with cancer and receiving chemotherapy, immunization rates were found to be very low. Main reason was the lack of recommendation by the primary physician involved in the treatment, mostly the oncologist. Awareness on this issue in physicians, particularly oncologists, may increase vaccination rates.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Medical oncologists’ attitudes towards vaccination in oncology practice

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Background: Despite of vaccination is a highly effective way of preventing certain infections and widely recommended in patients with cancer, vaccination rate are not high enough. The purpose of this study was to evaluate the attitude of medical
oncologists towards vaccination in their daily practice and predictors of vaccination practice in oncology.

Methods: A structured questionnaire is formed to evaluate the daily practice of vaccination. Medical oncologists actively working in Turkey were invited to study by emails, SMS messages and direct phone calls. Questionnaires were filled and the data were stored with an online survey platform.

Results: 273 medical oncologists participated the survey. Influenza, Pneumococcus and hepatitis B were the most commonly recommended vaccines (87.1%, 72.8%, 67.0%, respectively) in daily practice. Lung, lymphoma and breast cancer are the pathologies to which medical oncologists give priority while recommending vaccination (68.1%, 68.1%, 24.6%, respectively). Participants prefer to recommend vaccination to patients in remission/follow-up (68.4%) or before starting therapy (64.1%). Patients’ age and comorbidities were not related with rate of vaccination. Only 23.4% of the participants thought that their recommendations on vaccination were efficient and satisfying. Lack of time during outpatient clinic visit and lack of knowledge or experience about vaccination are the most common limitations during recommending vaccination.

There is a positive correlation between experience in the field and evaluating patients for vaccination ($r = 0.390$, $p < 0.001$), on the other hand, there is negative correlation between number of patients daily cared and evaluating patients for vaccination ($r = 0.390$, $p < 0.001$). Experience with autologous or allogeneic bone marrow transplant patients is related with more tendency to evaluate patients for vaccination ($p < 0.001$).

Conclusions: Status of experience in oncology, especially in bone marrow transplant units and total number of patients exposed daily are important predictors of vaccination practice in oncology. Similar with the data in other fields, there is also a huge heterogeneity in medical oncologists’ attitude towards vaccination.

Legal entity responsible for the study: N/A

Funding: Ankara University School of Medicine, Medical oncology - Medical Oncologists

Disclosure: All authors have declared no conflicts of interest.

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**Efficacy of influenza vaccine (FluVax) in patients on chemotherapy (POCT): final data analysis from South Australia**

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Background: Influenza (flu) virus infection has a significant morbidity and mortality in excess of 5-10% especially in patients with medical co-morbidities who are also immunosuppressed. Influenza vaccination decreases all-cause mortality by about 30-50%. Patients undergoing chemotherapy along with the general public are vaccinated annually; however, there has been no study to assess the efficacy of influenza vaccination in these groups (patients on chemotherapy - POCT).

Methods: This is a prospective single arm, phase II open label study. 53 POCT with non-haematological cancers were recruited between 2011 and 2012 influenza seasons. POCT vaccinated in the current influenza season were excluded. Participants had one non-haematological cancers were recruited between 2011 and 2012 influenza seasons.

Results: Primary endpoint was early seroconversion (SC) rate at 3weeks; other end-points were ≥ 2 years for A/Perth/16/2009 (H3N2); A/Perth/16/2009 (H3N2) 19 (39.58%) 26 (65%) 26 (59.1%) 21 (52.5%) B/Brisbane/60/2008 0 12 (30%) 12 (27.3%) 7 (17.5%) Virotech vaccination practice in oncology. Similar with the data in other fields, there is also a

Conclusions: POCT might have sub-optimal response to the FluVax. Our findings should be confirmed in a larger patient population and warrants further research into a more effective strategy in this patient group.

Clinical trial identification: ACTRN:12611000306910

Legal entity responsible for the study: Southern Adelaide Health Network Inc

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

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**Analysis of cancer outcomes after desensitization protocols in patients with metastatic disease**

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Background: Cancer chemotherapy and targeted therapy agents carry a potential risk for sensitization and induction of hypersensitivity reactions (HSR). It is widely unknown if patients who had drug reactions and underwent desensitization have different cancer outcomes, since the drug infusion time is largely extended. With this study we aim to describe patterns of HSR and overall survival (OS) rates for patients with metastatic cancer undergoing desensitization.

Methods: This is a single center retrospective observational cohort study. Primary endpoint was OS. All patients with stage IV colorectal (CRC), breast (BC) and ovarian cancer (OC) undergoing desensitization from 2008 to 2013 at our institution were included. All patients with mild to severe HSR (Brown’s classification) were desensitized at the Immunology and Allergy Unit using a 12-step protocol (6-hour infusion). Clinical pathological characteristics were tabulated according to type of primary. Proportion of patients alive at time points were obtained. Time to event outcomes were analyzed using Kaplan-Meier methods.

Results: 50 patients were included (14 BC, 17 CRC, 19 OC), 38 female and 12 male, the majority 50 years or older (n = 36, 72%) and with good performance status (Eastern Cooperative Oncology Group grade ≤1 in 94.6%, n = 45). Median follow-up from diagnosis of metastatic disease was 40 months for BC (interquartile range [IQR] 31.5-67.8), 41.8 months for CRC (IQR 29.3-68.1) and 33.3 months for OC (IQR 25.7-56.9).

Conclusions: Immune-related and adverse events following low versus high initial dose of Viscum album L. in cancer patients

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Background: Viscum album L. (VA, European mistletoe) is frequently used as an immunomodulatory agent alongside conventional therapies in cancer patients in Europe. VA has been associated with improvement in health-related quality of life and a reduction in chemotherapy related adverse drug reactions (ADRs). Mixed findings have been published regarding effects on overall survival. Beneficial effects of VA are believed to be related to its immunomodulatory properties. Recent evidence regarding immunotherapy in oncology has suggested an association between immune-related ADRs and beneficial outcomes. We investigated the immune-related events and ADR profiles related to VA therapy commencing with a low or high dose.

Methods: The medical records of 2393 cancer patients treated between 2000 and 2013 were assessed. Patients were retrospectively divided into two groups based on if their first VA application was low or high according to the appropriate Summary of Product Characteristics. Groups were compared by demographic, disease characteristics, details of treatment and ADRs.

Results: 967 patients received a low dose of VA on their first ever application and 1426 patients received a high dose. Groups did not differ by age, but significant differences were observed for gender, type and stage of cancer, type and administration of VA. Commencing VA therapy with a high dose was associated with a higher incidence of ADRs compared to commencing with a low dose (12.6% versus 0.7%). Adjusting for age, tumour site and stage produced an odds ratio of 36.8 (95% CI = 15.4-120.6, $p < 0.001$). Almost all ADRs, irrespective of dose, were of mild or moderate intensity (low: 100%, high: 94%). The majority of ADRs were immune-related, general disorders and administration site conditions (low: 80%, high: 92%), many of which were desired reactions, such as pyrexia and local reactions.

Conclusions: Commencing VA therapy with a high dose was highly associated with ADRs compared to a low dose, however, nearly all ADRs were expected, of mild to moderate intensity and most were desired reactions. Future research will investigate whether higher incidences of immune-related events are indicators of beneficial immunomodulation and thus better clinical outcomes.

Legal entity responsible for the study: Forschungsinstitut Havelhöhe, Gemeinschaftskrankenhaus Havelhöhe

Funding: Helios, Abahoa

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Compliance with oral cancer medications when dispensed in the oncology clinic vs. when provided directly by healthcare payers: a prospective multicenter study by the Oncoclinicas Group

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Background: The use of oral cancer medicines is rising in Brazil. In Brazil, after coverage was mandated in January 2014, oral cancer medications can be dispensed in the clinic where a patient is treated or directly by the healthcare payer (or by a payer-designated third-party).

Methods: We conducted an observational prospective multicenter study to compare compliance (primary endpoint) between patients who received their oral medications in oncology clinics versus those who received them directly from healthcare payers. Patients 18 years of age or older, receiving oral cancer treatment prescribed in any of the group’s 34 clinics were eligible. Patients filled in an anonymous questionnaire. Respondents were classified as ‘compliant’ when they answered ‘always’, ‘often’ or ‘frequently’ to the question: ‘Do you take this medication every day at the right time?’ Those who replied ‘sometimes’, ‘rarely’ or ‘never’ were classified as ‘non-compliant’. Further questions assessed different aspects related to adherence, including whether patients received their medication in a timely manner. Study protocol was approved by an independent ethics committee. Pearson chi-square was used to evaluate statistical significance with a 5% level.

Results: Between April 2015 and May 2016, 396 patients from 7 clinics entered the study: 126 (59,6%) received their medication at a cancer clinic and 160 (40,4%) directly from a payer. Median age was 57 years in both groups. Most patients were female and receiving hormone therapy. Non-compliance was higher in the group that received their medications directly from payers (19 patients, 11.9%, vs. 7 patients, 3.0%) when compared with those who received it in the clinic (p = 0.001). Moreover, 35% vs. 4.2% (p < 0.001) reported difficulties in acquiring their medicines, and 21.9% vs. 11.4% (p = 0.001) compared with those who received it in the clinic vs. when provided directly by healthcare payers.

Conclusions: Among patients treated in an oncology center, compliance was significantly higher when medications were dispensed by a healthcare provider instead of a pharmacy. This study suggests that, in Brazil, oral medication adherence can be improved by delivering medications directly to the patient, rather than through pharmacies.

Disclosures: All authors have declared no conflicts of interest.
Survival and functional outcomes of patients with metastatic solid organ cancer admitted to the intensive care unit of a general tertiary centre

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Background: Studies of survival outcomes in metastatic solid organ cancer patients admitted to the intensive care unit (ICU) are limited, with no documentation of functional status following discharge. Furthermore, despite the poor long term outcome, documentation of advance care planning, including goals-of-care (GOC), is often sub-optimal.

Methods: We retrospectively assessed outcomes from patients with incurable metastatic solid organ malignancies non-electively admitted to a tertiary hospital ICU from January 2010 - June 2015. Patient demographics were collected and survival rates analysed and correlated with potential prognostic factors. Post-discharge living arrangements and functional status as assessed by Eastern Cooperative Group (ECOG) at 1- and 3-months were collected. GOC documentation specifying resuscitation status were collected.

Results: 101 patients were treated in the ICU during the study period, with cancer treatment-related complications being the most common reason for admission (47%). The ICU, hospital, 30 day and 12 month mortality rates were 16%, 35%, 41% and 76%, respectively. On multiple-variable analysis, predictors of 30 day mortality were albumin <24 g/dL, ECOG ≥2 and sepsis, while only albumin <24 g/dL predicted for 1 year mortality (OR 7.50, 95% CI 1.53-36.9; p = 0.01). Median overall survival was 2.2 months (95% CI 1.0-3.5). 61% of patients had an ECOG score ≤1 within 4 months prior to ICU admission. Post-discharge functional status (ECOG ≥1) declined at 1 month (43%), but improved by 3 months (54%; p = 0.44) in surviving patients. 90% did not have an advanced care directive and 66% did not have a medical power of attorney.

Conclusions: Survival is poor in patients with metastatic cancer and non-elective ICU admissions, although functional status of surviving patients often recovers by 3 months. Low albumin and ECOG status are simple prognostic markers for mortality in cancer patients. Discussions around advanced care planning need to be made early to avoid inappropriate ICU admissions and interventions given the poor survival rates.

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Disclosure: All authors have declared no conflicts of interest.

The relation between the severity of breast cancer-related lymphoedema and quality-of-life

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Background: Breast cancer-related lymphoedema (BCRL) is a common problem that affects many breast cancer patients and may have a significant detrimental impact on their quality of life (QoL). The aim of the current study was to investigate the relation between the severity of BCRL and QoL of breast cancer patients. The study included 102 breast cancer patients, of whom 64% had clinically evident arm lymphoedema. BCRL was assessed by measuring the difference in circumference of upper limbs at four points (metacarpophalangeal joint, wrist and 10 cm above and below elbow). At each point the ratio of difference was calculated by dividing the difference in circumference by the circumference of the healthy arm. The sum of ratio differences was divided by 4 (mean arm circumference discrepancy [AICD]). BCRL was defined as an AICD ≥5%. The severity of arm lymphoedema was classified into grades 0 (no or <5% AICD), 1 (5-10% AICD), 2 (>10-30% AICD) and 3 (>30% AICD). QoL was assessed using the Functional Assessment of Cancer Therapy for Breast cancer patients with Lymphoedema (FACT-B + 4). The study included 102 breast cancer patients, of whom 64% had clinically evident arm lymphoedema. BCRL was assessed by measuring the difference in circumference of upper limbs at four points (metacarpophalangeal joint, wrist and 10 cm above and below elbow). At each point the ratio of difference was calculated by dividing the difference in circumference by the circumference of the healthy arm. The sum of ratio differences was divided by 4 (mean arm circumference discrepancy [AICD]). BCRL was defined as an AICD ≥5%. The severity of arm lymphoedema was classified into grades 0 (no or <5% AICD), 1 (5-10% AICD), 2 (>10-30% AICD) and 3 (>30% AICD). QoL was assessed using the Functional Assessment of Cancer Therapy for Breast cancer patients with Lymphoedema (FACT-B + 4).

Results: The average scores of the Functional Assessment of Cancer Therapy – General (FACT-G), Breast Cancer Subscale (BCS), Trial Outcome Index (TOI) and FACT-B + 4 differed significantly according to the presence of BCRL and its severity (Table). The lowest QoL scores were observed among patients with grade 3 BCRL.

Method: The study included 102 breast cancer patients, of whom 64% had clinically evident arm lymphoedema. BCRL was assessed by measuring the difference in circumference of upper limbs at four points (metacarpophalangeal joint, wrist and 10 cm above and below elbow). At each point the ratio of difference was calculated by dividing the difference in circumference by the circumference of the healthy arm. The sum of ratio differences was divided by 4 (mean arm circumference discrepancy [AICD]). BCRL was defined as an AICD ≥5%. The severity of arm lymphoedema was classified into grades 0 (no or <5% AICD), 1 (5-10% AICD), 2 (>10-30% AICD) and 3 (>30% AICD). QoL was assessed using the Functional Assessment of Cancer Therapy for Breast cancer patients with Lymphoedema (FACT-B + 4).
Cancer-related fatigue (CRF) is a complex multi-dimensional construct related to reduced physical function and health-related quality of life. This symptom is under-reported by patients and undertreated by clinicians. Recent reviews have concluded that exercise reduces cancer-related fatigue. The NCCN recommends that all cancer patients should be screened for fatigue regularly. As management of CRF is currently suboptimal, a change of approach is required.

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Methods: Breast cancer survivors who had finished their treatments in the last 6 months, did not have any evidence of disease and were able to manage the accelerometer were offered to participate in a cross sectional study. CRF was evaluated through PERFORM, a questionnaire developed and validated in Spanish speakers.

Conclusions: The results of the current study indicated a significant relationship between the severity of BCRL and QoL. This suggests that studies investigating the QoL of breast cancer patients should not only include BCRL as a dichotomous (absent/present) variable, but patients should be stratified according to the severity of BCRL as well.

Legal entity responsible for the study: Kaar Al Ain School of Medicine, Cairo University

Disclosure: All authors have declared no conflicts of interest.

Cancer-related fatigue in breast cancer survivors: more evidence for a physiological substrate

<table>
<thead>
<tr>
<th>Quality of Life Scale</th>
<th>Lymphedema grade</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-G</td>
<td>84 (17)</td>
<td>79 (16)</td>
</tr>
<tr>
<td>BCS</td>
<td>36 (8)</td>
<td>36 (8)</td>
</tr>
<tr>
<td>TOI</td>
<td>76 (15)</td>
<td>72 (12)</td>
</tr>
<tr>
<td>FACT-B + 4</td>
<td>120 (22)</td>
<td>114 (19)</td>
</tr>
</tbody>
</table>

Background: Cancer-related fatigue (CRF) is a complex multi-dimensional construct related to reduced physical function and health-related quality of life. This symptom is under-reported by patients and undertreated by clinicians. Recent reviews have concluded that exercise reduces cancer-related fatigue. The NCCN recommends that all cancer patients should be screened for fatigue regularly. As management of CRF is currently suboptimal, a change of approach is required.

Methods: Breast cancer survivors who had finished their treatments in the last 6 months, did not have any evidence of disease and were able to manage the accelerometer were offered to participate in a cross sectional study. CRF was evaluated through PERFORM, a questionnaire developed and validated in Spanish speakers. Weekly moderate-vigorous physical activity (WMVA) was objectively evaluated with accelerometers. Physical condition was evaluated through the one mile-walk test, hand-held dynamometer and sit to stand test.

Results: 96 women with a history of breast cancer were recruited between March - April 2016. Age 52 (29-78), BMI 26 (18-41), waist 86 cm (65-116). 72% had received adjuvant therapies. 17% Herceptin, 70% radiotherapy. Basal heart rate 74 bpm (56-102). Final heart rate (after walking one mile) 107 bpm (68-159); Estimated VO2max 27.7 ml/kg/min (7.7-47). Strength right upper extremity was 26 Kg (10-40). Sit to stand test 7,4 (4.1-18.4) s. WMVPA was 231 min (69.5-424.5). Median PERFORM score was 46 (12-06). There were not any significant correlations for previous treatments, physical condition, anthropometry or physical activity with fatigue score.

Heart rate (both basal and final) were significantly associated to fatigue (p < 0.05).

Conclusions: Despite meeting international recommendations for physical activity, this sample exhibited a poor cardiorespiratory fitness and cardiometabolic profile. Basal and post exercise heart rate were the only predictors of fatigue in our series. Neither previous treatments nor physical condition or adiposity signs had a definitive relationship with fatigue. Other authors have suggested that fatigue is associated with a maladaptive autonomic profile. Further research studying heart rate variability is warranted.

Legal entity responsible for the study: Hospital Universitario Puerta de Hierro-Majadahonda

Disclosure: All authors have declared no conflicts of interest.

Impact of cognitive functions on oral anticancer therapies adherence

Background: Oral anticancer therapies have now an important place in the therapeutic arsenal, but factors influencing adherence to oral treatment are poorly documented in oncology. The objective of this study was to assess the relationship between cognitive functions and oral medication adherence in order to identify patient profiles that are more likely to be non-adherents, with a focus on the elderly population particularly at risk.

Methods: This prospective pilot study included patients initiating a first exclusive oral therapy. Before initiation of treatment, we performed a standardized neuropsychological test battery and an assessment of autonomy, depression and anxiety. Information on socio-demographic conditions was collected. Adherence to oral therapy was evaluated by two self-assessment questionnaires and an observance sheet at 1 and 3 months after start of treatment. We present here only the results at 1 month.

Results: Among 126 patients enrolled, 111 (88%) completed the adherence questionnaires at 1 month with an adherence rate of 90% and a median age at baseline of 70. Global cognitive impairment was observed in 50% with the Montreal Cognitive Assessment (MoCA). Working memory disorders and depression were significantly associated with non-adherence: [1.38 (1.03-1.85); P= 0.0326] and [1.67 (1.11-19.59); P= 0.0032] respectively. A relationship was found between age and MoCA score and also with working memory impairment, with for both of them a higher impact above 70 years (P= 0.005).

Conclusions: Working memory dysfunctions and depression appear as predictors of non-adherence. Focusing on cognitive functions before initiation of oral anticancer therapy is therefore relevant to identify patients profiles more likely to fail self-management of oral anticancer therapy and therefore help decision-making, particularly in elderly.

Clinical trial identification: N0 ID-RCB: 2011-A00907-34

Legal entity responsible for the study: Professor Florence Joly

Disclosure: All authors have declared no conflicts of interest.

Evaluation of an interactive electronic patient reported outcome (e-PRO) system in outpatient with oral chemotherapy

Background: Health Information Technology (HIT) is increasingly integrated in clinical cancer care. Simultaneously routine assessment of patient reported outcomes (PROs) has been shown to reliably improve symptom management, identification of psychosocial problems and patient-provider communication.

Methods: This study is a single center experience of a multicenter randomized study on the development and validation of an interactive e-PRO tool (RemeCoach). After obtaining informed consent, outpatients, using oral anti-cancer treatment, recorded their medication intake and 17 clinical parameters using this E-PRO tool. The device allowed real time data collection and communication with other care providers via a central platform. The registered data were processed by an algorithm, this algorithm stratifies the data into different grades according to international standards of care (CTCAE v4.0) and clinical importance. Patient clinical and demographic information is collected from medical records and analyzed using descriptive statistics.

Results: 37 Patients were included, 59% male, mean age 59.2 (range 38-79). 35% Of patients used capecitabine, 43% regorafenib, 5% pazopanib, 5% erlotinib and 5% sunitinib. Most common symptoms cited were fatigue, cutaneous toxicity, myalgia and joint pain and cough. Out of 19 patients that stopped therapy, one (5%) dropped out of the study. 1, switched therapy due to progressive disease, 8 (42%) patients died, 9 (48%) terminated prescribed treatment. The RemeCoach was well adopted: > 75% patients registered >75% of clinical outcomes.

Conclusions: This study confirms the feasibility of the program, in an outpatient setting. This e-tool provides a means to register compliance, early symptoms of disease and toxicity of treatment. The compliance to the e-PRO tool will be confirmed, with further development of this program in a multicenter, randomized design. Evaluation of quality of life PRO-measurements and further exploration of the relationship between optimal pharmacovigilance and improvement of patient’s outcome will ensue.

Legal entity responsible for the study: University Hospital Antwerp

Disclosure: All authors have declared no conflicts of interest.
Background: The incidence of renal insufficiency is ever increasing in cancer patients, since patients are getting older and more aggressive treatments become available. For those drugs in which renal excretion is an important determinant of elimination, dose adjustment is often required if renal function is impaired. “CS rules” is a cognitive clinical decision support system (CDSS) designed to assist clinical pharmacists in making dosing decisions for individual patients. Recommendations on chemotherapy dosing are consistent with the established guidelines and published evidence.

Methods: From September 2015 until January 2016 a pilot with the CDSS was performed in the ZGT Hospital in the Netherlands. Clinical rules were defined for 18 cytotoxic drugs used in our hospital, for which dose reduction is required if renal function is impaired. The CDSS was run overnight and generated alerts on all newly prescribed chemotherapeutics. Alerts were analyzed by the clinical pharmacist. If a dose reduction seemed necessary, the oncologist was contacted by the pharmacist and the necessity of dose reduction was discussed.

Results: During the pilot period a total of 2681 chemotherapeutics were prescribed, the 18 active rules generated 112 alerts. Overall, 18.8% of the generated clinical alerts were discussed by the clinical pharmacist or oncologist. If a clinical alert was recognized by the clinical pharmacist, a recommendation was sent to the prescribing oncologist who decided whether to carry out the suggested intervention or not.

Conclusions: CDSS can effectively be used in daily hospital pharmacy practice to select patients at risk of cytotoxic drug overdose due to renal impairment. The identification of patients at risk helps the clinical pharmacist and oncologist to optimize drug therapy in cancer patient with renal dysfunction.

Legal entity responsible for the study: ZGT Hospital

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Table: Detailed overview of number of prescription, alerts, and interventions per cytotoxic drug

<table>
<thead>
<tr>
<th>Cytotoxic drug</th>
<th>Prescriptions</th>
<th>Alerts</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>452</td>
<td>14</td>
<td>3.1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>133</td>
<td>27</td>
<td>20.3</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>482</td>
<td>3</td>
<td>0.62</td>
</tr>
<tr>
<td>Capcitabine</td>
<td>429</td>
<td>22</td>
<td>5.1</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>395</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Irsogladine</td>
<td>64</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>285</td>
<td>13</td>
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<tr>
<td>Fluorouracil</td>
<td>1</td>
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<td>Ifosfamide</td>
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<td>Hydroxyurea</td>
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<td>0</td>
</tr>
<tr>
<td>Imitinamide</td>
<td>96</td>
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<td>0</td>
</tr>
<tr>
<td>Lomustine</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Methotrexate</td>
<td>56</td>
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<td>28.6</td>
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<tr>
<td>Pemetrexed</td>
<td>214</td>
<td>13</td>
<td>6.1</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>2681</td>
<td>112</td>
<td>4.1</td>
</tr>
</tbody>
</table>

* as a percentage of number of prescriptions
* as a percentage of alerts
* 4 alerts were generated after a single prescription of fluorarabin

Conclusions: CDSS can effectively be used in daily hospital pharmacy practice to select patients at risk of cytotoxic drug overdose due to renal impairment. The identification of patients at risk helps the clinical pharmacist and oncologist to optimize drug therapy in cancer patient with renal dysfunction.

Legal entity responsible for the study: ZGT Hospital

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Drug-drug interactions in cancer patients: a prospective study of medication surveillance on cytotoxic agents


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Background: Cancer patients are often treated with numerous concomitant medications other than antineoplastic agents. Recent studies have shown a high prevalence of drug interactions (DDIs) among these patients, some of them are clinically relevant due to potential changes on the efficacy and toxicity of the anticancer therapy. We aimed to determine clinically relevant DDIs leading to pharmaceutical intervention in ambulatory cancer patients treated at our centre.

Methods: A sample size of 149 subjects was calculated based on an expected percentage of 11% of patients with clinically relevant DDIs. Patients starting a new anticancer therapy were asked to participate in this trial. Information of the use of concomitant medications with antineoplastic agent(s), including over-the-counter drugs, was collected by the oncologist through a structured interview. DDIs were identified using the LexiComp Handbook and a software programme available at www.drugs.com. If a clinically relevant DDI was recognized by the clinical pharmacist, a recommendation was sent to the prescribing oncologist who decided whether to carry out the suggested intervention or not.

Results: The mean age of the patients was 57.5 ± 13.6 years, and 74.5% (n = 111) of them were female. The majority of patients had solid tumours (98.6%), specifically breast (53.7%), followed by gastrointestinal (23.5%) and genitourinary malignancies (6.7%). Seventy-two patients (47.7%) had an underlying comorbidity other than cancer, mainly high blood pressure (n = 52) and diabetes mellitus (n = 23). The median number of medications per patients was 3 (range: 1 – 12). A total of 37 clinically relevant interactions were detected in 26 patients (17.4%, 95% Confidence Interval: 14.3 – 20.5). Of these interactions, 11 (29.7%) were considered of high risk (category D), leading to therapy modifications in 100% of cases, as suggested by the clinical pharmacist. The principal mechanism of DDIs was pharmacokinetic (70.3%), followed by pharmacodynamic (19%), and unknown in the remaining cases (10.7%).

Conclusions: Clinically relevant DDIs were frequently detected in this prospective study. A multidisciplinary approach is required to identify and avoid potentially harmful DDIs.

Legal entity responsible for the study: University of Costa Rica. Caja Costarricense de Seguro Social.

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Disclosure: All authors have declared no conflicts of interest.

Impact of adjuvant anthracycline-based and taxane-based chemotherapy on plasma VEGF levels and cognitive function in early-stage breast cancer patients

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Abstract: Vascular endothelial growth factor (VEGF) has been shown to induce neurogenesis in the brain and yield neuroprotective effects. It is hypothesized that adjuvant chemotherapy containing doxorubicin or taxane, reduces circulating VEGF levels and, in turn, leads to cognitive decline in cancer patients who receive chemotherapy. This multicenter, longitudinal study was designed to evaluate the impact of chemotherapy on VEGF levels and the association between VEGF levels and cognitive function.

Methods: One hundred and forty-six early-stage breast cancer patients were recruited and assessed at three time points: before chemotherapy (T1), during chemotherapy (T2) and at the end of chemotherapy (T3). At each time point, we quantified plasma VEGF levels using a multiplex immunosay (Luminex®). Self-perceived cognitive functioning was assessed using the Functional Assessment of Cancer Therapy-Cognitive Function Version, and objective cognitive functioning was assessed using Headminder®. Plasma VEGF levels were quantified using a multiplex immunosay (Luminex®).

Results: The average age of this cohort was 50.5 ± 9.2 years, with the majority being Chinese (82.9%), and diagnosed with Stage II breast cancer (56.2%). Forty-one (28.3%) patients reported self-perceived cognitive impairment at the end of chemotherapy, with impairment in the attention (7.2%) and memory (11.0%) domains detected using Headminder®. Among the patients who received an anthracycline-based chemotherapy regimen, the median plasma VEGF levels were significantly higher at T2 (T2: 37.0 pg/ml vs T1: 21.2 pg/ml; p < 0.001) and T3 (T3: 36.4 pg/ml vs T1: 21.2 pg/ml; p < 0.001) than at baseline. Among the patients who received taxane-based chemotherapy, there were no significant differences in VEGF levels between the time points. Plasma VEGF levels were not associated with chemotherapy-associated cognitive impairment.

Conclusions: Breast cancer patients experience dysregulation in plasma VEGF levels during chemotherapy, and the regimen types may have a differential impact on circulating VEGF levels. However, changes in plasma VEGF levels during chemotherapy were not associated with cognitive impairment.

Legal entity responsible for the study: SingHealth GIRC, National Cancer Centre Singapore

Funding: National Medical Research Council Singapore

Disclosure: All authors have declared no conflicts of interest.
Insomnia prevalence in an oncology patient population: an Irish tertiary referral centre experience

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Background: NCCN survivorship guidelines recommend dedicated sleep assessment reflecting its association with increased symptom distress scores and mortality. Reported insomnia prevalence in the general Irish population is 15%. Reported prevalence internationally amongst new or recently diagnosed cancer patients varies from 23-50%. Insomnia prevalence has not been quantified in an Irish oncology cohort.

Methods: With ethical approval an 8 page questionnaire was prospectively administered to ambulatory cancer patients aged ≥ 18 attending a tertiary referral centre. Pre-specified criteria for insomnia syndrome (IS) included those of the International Classification of Sleep Disorders and DSM-IV. The Hospital Anxiety and Depression scale (HADS-D/A) was used to screen for depression and anxiety as confounding variables. Logistical regression model was used for analysis.

Results: Response rate was 87% (294/337). Median respondent age was 55-64.80% were female. Breast (37%), colorectal (13%) and lung (12.2%) were the most common cancer subtypes. 62% reported sleep disturbance after diagnosis 33.7% met IS criteria. 60% reported moderate/severe insomnia related distress. 23% a significant impact on physical function. 45% who did not meet criteria had 2 of 4 critical features. On univariate analysis female sex, age <65, cancer subtype, alcohol consumption, HADS-D/A ≥11 were associated with statistically significant higher odds ratios (OR) of IS. Multivariate analysis identified breast cancer (OR 3.17; p = 0.01), age <65 (OR 1.8; p= 0.03) and alcohol consumption (OR 1.9; p= 0.01) as independent predictors of IS. Interestingly, 45% were unaware that alcohol consumption could impact on sleep. 62% of patient management should incorporate sleep assessment. 34% recalled such assessment. Written information (29%) was favoured over pharmacological.

Conclusion: Insomnia prevalence in this Irish cohort is comparable to that previously reported and sleep assessment is justified. Alcohol is a modifiable risk factor independently predicting IS. HADS-D/A ≥11 increased OR of IS demonstrating additional utility of this scale. A patient education leaflet on sleep management is in progress to incorporate and reinforce our findings.

Legal entity responsible for the study: Dr Emily Harrold

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

Social supports for patients with cancer in Ireland

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Background: A sizable but controversial literature describes a direct relationship between high levels of social support and improved clinical outcomes in cancer patients. There is however, limited data on social supports/networks among pts with cancer in Ireland.

Methods: Pts with a cancer diagnosis on active treatment or in follow-up in the South East Cancer Centre in Ireland were eligible. Pts completed a questionnaire which included, demographics, social networks measurement using the Berkman-Syme Social Networks Index (SNI) classifying pts into 4 categories (1 to 4), instrumental support using the tangible support component of the Medical Outcomes Study Social Support Survey (MOS-SS) and informational/support incorporating questions on the availability and ability to use a computer with internet access, the use of the internet to seek cancer information/link with other patients. Subgroups studied included gender and age (≤70 and >70 yrs).

Results: 188/237 pts completed the questionnaire (response rate 79%) with the following characteristics: female (n=125, 67%), age ≥70 yrs (n = 73, 39%). The commonest/cancer was breast (n = 61, 38%) and 35% had education beyond secondary level. SNI was evaluable in 187 pts of whom 34 (18%) were socially isolated (SNI category 1). Men were more likely to have low social networks (SNI < category 3) than women; p = 0.04, with no difference between older and younger pts; p = 0.88. The mean score for the tangible component of the MOS-SS for all pts was 85.3(pd 21.1) which was similar between all subgroups. 128 pts had a computer with internet access at home (69%). 37% (n=27) elderly pts were able to use the computer compared to 78% (n= 80) younger pts (p < 0.001). 34% (n=25) elderly pts were able to use the Internet compared to 78% (n = 89) younger pts (p < 0.001). 52% (n = 91) patients used the computer to access information and only 9%(n = 16) used the computer to link with other patients through support groups / blogs.

Conclusions: Social isolation in this population was high at 18%, more commonly reported in male patients. While social media creates an opportunity to support isolated patients, only a third of older patients are computer/internet proficient in this population.

Legal entity responsible for the study: Anne Horgan

Funding: University Hospital Waterford

Disclosure: All authors have declared no conflicts of interest.

The prospective study of relation between 5-HIAA/ substance P and nausea/vomiting in patients receiving moderately emetogenic chemotherapy

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Background: The use of antagonists of the NK1 and/or 5-HT3 receptor is recommended for the patients receiving high emetogenic chemotherapy (HEC) in order to prevent chemotherapy-induced nausea and vomiting (CINV). Although we widely use them for the patients receiving moderately emetogenic chemotherapy (MEC), supporting evidence is insufficient. We therefore planned to measure the blood concentration of 5-HIAA and substance P in patients receiving MEC, and investigate the relation between their levels and CINV.

Trial design: This is a multicenter exploratory observational research in Japanese patients receiving chemotherapy for gastrointestinal cancer. The key eligibility criteria are as follows: 1) Diagnosed gastrointestinal cancer; 2) Planned to receive high-dose cisplatin (for five patients in cohort 1, for validation of measurement), oxaliplatin or irinotecan (for 45 patients in cohort 2); 3) >20 years of age or older; 4) ECOG PS of 0, 1 or 2; 5) Keeping adequate major organ function. By sampling the patients’ blood before and 4, 24, 48, 72 and 96 hours after HEC/MEC administration, we measure the
changes in blood concentration of substance P and 5-HIAA after chemotherapy, and survey the relevance of blood concentrations of substance P and 5-HIAA and CINV measured by visual analogue scale. This trial is recruiting the patients from 3 institutes from February 2016 to October 2017, and registered as UMIN000021072.

Clinical trial identification: The trial information of this study was registered as UMIN000021072 and released 18th February 2016.

Legal entity responsible for the study: Hokkaido University Hospital

Funding: Otsuka Pharmaceutical Co., Ltd.


Quality of life, efficacy, and patient-reported outcome with NEPA as antiemetic prophylaxis in patients receiving highly or moderately emetogenic chemotherapy

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Background: The combination of 5-HT3- and NK1-receptor-antagonists (RA) and dexamethasone is recommended by international guidelines for patients receiving highly emetogenic (HEC) and anthracyline / cyclophosphamide (AC) containing chemotherapy (MEC) regimens for the prevention of chemotherapy-induced nausea and vomiting (CINV). NEPA (Akynzeo®) is a fixed combination capsule that combines the new NK1-RA netupitant and the 5-HT3-RA palonosetron. It has been approved for the prevention of acute and delayed CINV in adult cancer patients receiving cisplatin-based HEC or MEC. The objective of the study is to evaluate the quality of life of adult cancer patients undergoing MEC or HEC and receiving NEPA for CINV prophylaxis and to investigate the efficacy and safety of NEPA under real life conditions.

Trial design: This non interventional study is planned to evaluate 2500 patients receiving single day or two day MEC or HEC (10-20 patients / participating center) in > 100 German centers (min. 125, max. 250 centers). NEPA is prescribed for the prevention of acute and delayed CINV in adult cancer patients receiving cisplatin-based HEC or MEC. The primary endpoint is the patients quality of life as recorded by FLIE questionnaires. Secondary endpoints include complete response (CR, no vomiting, no rescue medication), additional medication, safety data and AEs as documented by online questionnaire and patient diary: 3 consecutive chemotherapy cycles will be documented. For documentation treating physicians use the ODM QuaSi® online documentation system. All specifications in the online documentation system must be verifiable by patient records or medical test records. The trial is in ongoing. At the time of abstract submission, 178 patients treated in 129 centers (69 gynaecologic oncology, 58 medical oncology, 2 urologic oncology) had been included. The majority of patients (118) had breast cancer. Data on quality of life, efficacy and toxicity as available at the cut-off date May 2016 will be presented at the meeting.

Clinical trial identification: DRKS000009316

Legal entity responsible for the study: Riemser Pharma GmbH

Funding: Riemser Pharma GmbH

Disclosure: M. Karthaus: Consultant for Helios Healthcare, Riemser Pharma. J. Schilling: Consultant of Riemser Pharma. All other authors have declared no conflicts of interest.

Validation of a risk-assessment score for prediction of venous thromboembolism in cancer outpatients receiving active treatment: ONKOTEV 2 trial

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Background: Venous thromboembolism (VTE) risk assessment is an outstanding area of investigation. In a previous large prospective study, involving more than 800 ambulatory cancer patients from two European academic institutions, we pioneered an extensive screening with a upper and lower limbs ultrasound to all patients to have the most precise incidence of VTE in cancer outpatients (ONKOTEV trial - data under submission). We investigated several risk factors potentially associated to a increased risk of thrombosis and tested the efficacy of Khorana score in preventing VTE events. We finally constructed a four-cathgory risk model score, improving the predictability of VTE in cancer outpatients. The four variables included in the ONKOTEV score are the following: the presence of metastases, a positive history of previous VTE, the macroscopic compression of vessels or lymphnodes by tumor mass and a Khorana score point of 2 or more. The validation of this new risk assessment model is the goal of the further prospective trial, ONKOTEV 2.

Trial design: ONKOTEV 2 trial is an observational, multicentric, no-profit study, endorsed by EORTC Young Investigator Program, and aims to validate the ONKOTEV score as novel easy-to-use tool for the prediction of VTE in ambulatory cancer patients starting a new antitumoral treatment (chemotherapy, endocrine therapy, radiation therapy or surgery). The study will be based on clinical, laboratory and imaging data collection, which will allow to calculate the ONKOTEV score in each patient at baseline. The patient will be clinically monitored for 8 months, in order to detect any thromboembolic event during the trial. The duration of the study will be approximately 20 months. It will be a first analysis at the time of the visit inclusion (T0), a control visit at 8 months (T8). The median period of observation will be 8 months. It is expected to enroll 465 patients.

Legal entity responsible for the study: Study coordination: European Institute of Oncology

Funding: EORTC

Disclosure: All authors have declared no conflicts of interest.
Abstracts

Quality of respection and outcome in stage III thymic epithelial tumors (TET): A retrospective analysis of 150 cases from the national network RYTHMIC experience


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Background: Stage III TET represents a heterogeneous population and their optimal approach remains unclear; most of the available literature is composed of small series spanning over extended periods of time. RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a French nationwide network for TET with the objective of territorial coverage by regional expert centers and systematic treatment decision of patients management at national tumor board. We reviewed our experience in stage III thymic tumors in order to evaluate the value of tumor board recommendations and multidisciplinary approach.

Methods: We conducted a retrospective analysis of patients (pts) with stage III TET discussed at the RYTHMIC tumor board from January 2012 to December 2015. Clinical, pathologic and surgical data were prospectively collected in a central database. Survival rates were based on Kaplan-Meier estimation. Cox proportional hazard models were used to evaluate prognostic factors for disease free survival (DFS) and overall survival (OS).

Results: 150 pts were included in the analysis. Median age was 64 years [18 – 91], 56% males, thymoma A-B2/ B3 thymic carcinoma in 52% and 47% respectively; 12% presented with autoimmune disorder (76% myasthenia). Local treatment was surgery in 134 pts (90%) followed by radiotherapy (RT) in 90 pts; 26 pts received preoperative chemotheraphy (CT). Complete respection rate (R0) was 53%. Among 38 pts considered non-surgical candidates at diagnosis, 26 pts became resectable after induction CT with a R0 rate of 58%, 12 pts received CT-RT and/ or CT as primary treatment. Recurrence rate was 38% (n = 57), first sites were pleural (n = 32) and lung (n = 12). The 5-year OS and DFS were 88% and 32% respectively. Gender (p = 0.04), histology (p = 0.02) and surgery (p < 0.001) as primary treatment modality were significant prognostic factors for OS in multivariate analysis. Histology (p = 0.02) and adjuvant RT (p = 0.05) were significantly associated with DFS. Completeness of resection was not associated with survival in our cohort.

Conclusions: Surgery followed by radiotherapy improves outcome irrespectively of R0. Stage III TET not candidate to surgery should be reassessed for resection after induction chemotherapy.

Legal entity responsible for the study: N/A
Funding: RYTHMIC
Disclosure: All authors have declared no conflicts of interest.

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Background: RYTHMIC (Réseau tumeurs THYMéques et Cancer) is a nationwide network for TET appointed in 2012 by the French National Cancer Institute. The objectives of the network are management of clinical tumor board and central histopathological review of all cases. RYTHMIC Tumor Board is based on initial histopathological diagnosis.

Methods: Pathological central review of patients diagnosed with TET from January 2012 to May 2016 was made by a panel of 10 expert pathologists from the working group. Assessment of agreement or disagreement between the initial institution and the panel review was made according the WHO 2004/2015 and new ITMIG proposals for histologic typing and staging. Disaccords were classified as "major" when they would have changed the therapy or management of patients according to the RYTHMIC guidelines.

Results: A total of 400 specimens were reviewed. Considering either histological subtype and/or staging, a total of 172 discordances in 157 patients (39%) were identified: 111 concerning histological diagnosis and 61 regarding stage. A total of 31 major discordances in 29 patients (7%) were identified: 18 patients for whom management of disease should have changed the therapy or management of patients according to the panel review was made according the WHO 2004/2015 and new ITMIG proposals for histologic typing and staging.

Conclusions: The RYTHMIC experience confirms the relevance of an expert histopathological panel diagnosis of thymic malignancies and for better decision-making in particular concerning post-operative radiotherapy to avoid over- or under-treatment of the patients.

Legal entity responsible for the study: N/A

Funding: RYTHMIC

Disclosure: All authors have declared no conflicts of interest.

Table 1511P Main outcomes of the considered pivotal phase III RCTs in first-line for advanced NSCLC with activating EGFR-mutations and the corresponding ESMO-MCBS score

<table>
<thead>
<tr>
<th>Authors/Trial</th>
<th>Regimens of comparison</th>
<th>N of patients</th>
<th>Primary endpoint</th>
<th>OS (months)</th>
<th>PFS (months)</th>
<th>p-Value*</th>
<th>PFS/OS gain (months)**</th>
<th>PFS/OS HR (95% CI)**</th>
<th>ESMO-MCBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al, 2011 OPTIMAL</td>
<td>carboplatin + gemcitabine + erlotinib</td>
<td>72</td>
<td>PFS</td>
<td>NR</td>
<td>4.6</td>
<td>&lt; 0.001</td>
<td>8.5</td>
<td>0.16 (0.10-0.26)</td>
<td>4</td>
</tr>
<tr>
<td>Rosell et al, 2012 EURTAC</td>
<td>carboplatin + docetaxel + gemcitabine + erlotinib</td>
<td>129</td>
<td>PFS (crossover allowed)</td>
<td>21.6</td>
<td>6.3</td>
<td>&lt; 0.001</td>
<td>3.2</td>
<td>0.48 (0.36-0.64)</td>
<td>4</td>
</tr>
<tr>
<td>Mammoto et al, 2010</td>
<td>carboplatin + paltuxizum + gemcitabine</td>
<td>110</td>
<td>PFS</td>
<td>23.6</td>
<td>5.5</td>
<td>&lt; 0.001</td>
<td>4.9</td>
<td>0.36 (0.25-0.51)</td>
<td>3</td>
</tr>
<tr>
<td>Mitsudomi et al, 2010</td>
<td>carboplatin + docetaxel + erlotinib</td>
<td>114</td>
<td>PFS</td>
<td>30.5</td>
<td>10.4</td>
<td>&lt; 0.001</td>
<td>2.9</td>
<td>0.49 (0.37-0.71)</td>
<td>3</td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>carboplatin + gemcitabine + gefitinib</td>
<td>86</td>
<td>OS</td>
<td>22.9</td>
<td>6.3</td>
<td>&lt; 0.001</td>
<td>3.2</td>
<td>0.93 (0.72-1.21)</td>
<td>1</td>
</tr>
<tr>
<td>Han et al, 2012</td>
<td>carboplatin + gemcitabine</td>
<td>26</td>
<td>PFS (crossover allowed)</td>
<td>22.3</td>
<td>8.0</td>
<td>&lt; 0.001</td>
<td>4.9</td>
<td>0.49 (0.37-0.65)</td>
<td>4</td>
</tr>
<tr>
<td>LUX Lung 3</td>
<td>carboplatin + gemcitabine + erlotinib</td>
<td>111</td>
<td>OS</td>
<td>NR</td>
<td>6.9</td>
<td>&lt; 0.001</td>
<td>3.4</td>
<td>0.28 (0.20-0.39)</td>
<td>3</td>
</tr>
<tr>
<td>Wu et al, 2014 LUX-Lung 6</td>
<td>carboplatin + gemcitabine</td>
<td>122</td>
<td>PFS</td>
<td>NR</td>
<td>5.6</td>
<td>&lt; 0.001</td>
<td>3.4</td>
<td>0.28 (0.20-0.39)</td>
<td>3</td>
</tr>
</tbody>
</table>
Results: Univariate analysis showed ESCC patients with higher FGFR1 mRNA expression had significantly shorter overall survival (OS: 22.00 vs 33.00 months; P = 0.037). However, the analysis of pooled data from TCGA indicates there is no significant association between FGFR1 mRNA expression and OS in ESCC patients (25.10 vs 25.07 months; P = 0.477). Either in our local or TCGA data sets, no significance correlation between FGFR1 mRNA expression and disease free survival (DFS) was found (21.10 vs 39.00 months, P = 0.413, 18.10 vs 21.22 months; P = 0.334). Pooled analyses of TCGA datasets showed FGFR1 amplification was found in 13/186 (6.98%) of all patients and was more frequent but without significant difference in squamous cell carcinoma than that in adenocarcinoma (10.31 % vs 3.37 %; P = 0.064). Survival analysis showed ESCC with FGFR1 amplification had no significantly difference in OS (25.47 v 35.80 months; P = 0.499) than those without FGFR1 amplification.

Conclusions: Our analyses results support FGFR1 mRNA expression but not amplification could be an independent prognostic biomarker in patients with surgically resected ESCC.

Legal entity responsible for the study: Junxun Xue
Funding: West China Hospital
Disclosure: All authors have declared no conflicts of interest.

1514P  Preoperative diffuseing capacity correlates with tumor malignant grade and surgical outcome in clinical stage I lung cancer
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Background: Diffusing capacity of the lung for carbon monoxide (DLCO) is a predictor of complications after resection for lung cancer. This study aimed to determine the association between DLCO and tumor aggressiveness and survival in clinical stage I non-small cell lung cancer (NSCLC) patients.

Methods: We retrospectively examined 437 consecutive patients with clinical stage IA NSCLC who underwent complete resection between January 2009 and December 2014 at our institution. Patients were divided into 2 groups according to preoperative DLCO value. Several potential prognostic factors including DLCO were analyzed with respect to outcomes.

Results: The median follow-up periods after the operations were 39.0 months (1.0 - 99.0 months). Total 53 patients with 50% or less of DLCO and 384 patients with more than 50% of DLCO were compared. Patients with low DLCO were more male (77% vs 58%), higher age (73.5 ± 8.0 vs 66.7 ± 9.8), higher smoking history (93% vs 52%) compared with patients with high DLCO. The incidence of adenocarcinoma was low in patients with low DLCO (51% vs 84%), whereas the incidence of squamous cell carcinoma was high (40% vs 9%) compared to patients with high DLCO. 19% of adenocarcinoma patients with low DLCO were lepidic predominant, whereas 31% with high DLCO. The OS and DFS decreased to 68.3% and 63.7% at 5 years in patients with low DLCO, compared with 92.3% and 85.2% in patients with high DLCO (P < 0.001, log-rank, respectively). Multivariate survival analysis using Cox’s regression model revealed that less than 50% of DLCO was an independent predictor for OS (hazard ratio 4.21; P = 0.001) and DFS (hazard ratio 3.44; P = 0.001).

Conclusions: Preoperative DLCO correlated with tumor malignant grade and was an independent determinant of long-term survival in patients with clinical stage I NSCLC who were amenable to curative surgery.

Legal entity responsible for the study: N/A
Funding: Hiroshima University
Disclosure: All authors have declared no conflicts of interest.

Table 1514P – Median wait times for investigation and treatment

<table>
<thead>
<tr>
<th>Relative wait times from:</th>
<th>Recommended time, days</th>
<th>Median time, days (IQR)</th>
<th>Patients within target, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation (n = 511)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referral to first appointment (n = 551)</td>
<td>14</td>
<td>6 (4-10)</td>
<td>461 (84%)</td>
</tr>
<tr>
<td>Referral to chest computed tomography scan (n = 189)</td>
<td>14</td>
<td>5 (1-7)</td>
<td>174 (92%)</td>
</tr>
<tr>
<td>Biopsy to pathology result (n = 551)</td>
<td>14</td>
<td>3 (2-4)</td>
<td>530 (99.0%)</td>
</tr>
<tr>
<td>Request for EFR and ALK testing to result (n = 172)</td>
<td>14</td>
<td>5 (3-6)</td>
<td>169 (98%)</td>
</tr>
<tr>
<td>Treatment (n = 379)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory consultation to time of surgery (n = 210)</td>
<td>56</td>
<td>59 (41-80)</td>
<td>100 (48%)</td>
</tr>
<tr>
<td>Operative decision to time of surgery (n = 210)</td>
<td>28</td>
<td>21 (12-31)</td>
<td>180 (86%)</td>
</tr>
<tr>
<td>Surgery to commencing adjuvant chemotherapy (n = 42)</td>
<td>120</td>
<td>44 (36-55)</td>
<td>45 (98%)</td>
</tr>
<tr>
<td>BO referral to BO consultation (n = 211)</td>
<td>7</td>
<td>4 (2-7)</td>
<td>166 (79%)</td>
</tr>
<tr>
<td>BO referral to commencing definitive radiation (n = 67)</td>
<td>28</td>
<td>26 (22-35)</td>
<td>42 (63%)</td>
</tr>
<tr>
<td>Diagnosis to commencing definitive chemotherapy (n = 96)</td>
<td>100</td>
<td>27 (13-54)</td>
<td>48 (100%)</td>
</tr>
<tr>
<td>BO referral to commencing palliative radiation (n = 67)</td>
<td>14</td>
<td>8 (6-16)</td>
<td>69 (72%)</td>
</tr>
<tr>
<td>Decision for chemotherapy to commencing chemotherapy (n = 117)</td>
<td>7</td>
<td>6 (4-8)</td>
<td>78 (68%)</td>
</tr>
</tbody>
</table>

IQR: interquartile range; EFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; BO: radiation oncology

1515P Frequency, patterns and prognostic impact of distant metastases in a large mono-institutional series of malignant pleural mesothelioma (MPM): Not necessarily bad news

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Background: MPM is a deadly cancer whose lethality is almost invariably due to thoracic loco regional progression, whereas distant metastasis (mets) are rarely reported and their prognostic impact remains unclear. The aim of this study is to describe the incidence and patterns of metastatization and to explore their potential prognostic role in a large series of MPM patients (pts) in the highly asbestos polluted area of Casale Monferrato, in the North of Italy.

Methods: Data from a dedicated MPM database were retrieved and analyzed with MedCalc Statistical Software version 16.1.

Results: From 2009/1 to 2016/1, 368 pts (118 females, 250 males), median age 70.5 (range 28 – 91, IQR 63 – 77) were treated at our institution. Pts characteristics were as follows: asbestos exposure certain professional in 147 (40%), certain domestic in 51 (14%), environmental in 170 (56%), PS 0 in 239 (75%), 1 in 95 (26%), 2 in 2 in 34 (9%).
Chemotherapy-naïve patients with stage IIIB, IV, or recurrent NSq-NSCLC, Methods: NSq-NSCLC.

Conclusions: Eighteen % of pts in this series had distant mets, mainly in lung, liver, peritoneum and bone. Distant mets are rarely found at diagnosis (3.5%) but usually are a late event and develop at approximately two-thirds of the natural history of MPM. Acknowledging the limits of the small numbers, our results suggest that distant disease likely does not negatively affect OS compared with loco-regional progression. The longer OS of distant mets patients may indeed suggest a better controlled or a less aggressive thoracic disease.

Legal entity responsible for the study: General Director of ‘SS. Antonio e Biagio e C. Aringo’ Hospital, Dr. Giovanni Baraldi

Disclosure: All authors have declared no conflicts of interest.

1518P Malignant pleural effusion (MPE) characterized with 11C-Methionine PET/CT before and after talc pleurodesis: interim evaluation of a prospective clinical trial

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Background: Malignant pleural effusion (MPE) is the one the most frequent signs of mesothelioma presentation. 18F-FDG PET/CT has proved to be useful in detecting pleural lesions, although unreliable results have been reported in patients receiving talc pleurodesis due to induced inflammatory reaction. In this study we aimed to define the role of 11C-methionine PET/CT in the characterization of MPE before and after talc pleurodesis.

Methods: From September 2014 to February 2016 30 consecutive patients referred to our Institution for MPE were prospectively enrolled. Patients were evaluated at baseline and after pleurodesis with two consecutive PET investigations: 11C-methionine (experimental) and 18F-FDG (standard). Semi-quantitative PET parameters were defined for both examinations: i.e. SUVmax, SUVmean, metabolic tumor volume (MTV) and metabolic tumor burden (MTB = MTVxSUVmean), and statistically compared to pathological findings at videothoracoscopy.

Results: The interim analysis was completed in 15 patients (M=13; mean age 73 years) affected by malignant mesothelioma (12 epithoeloid, 3 non-epithoeloid). All tumors showed increased uptake of 11C-methionine at baseline: median SUVmax, SUVmean, MTV and MTB were 4.7 (range 3-10.1), 2.8 (range 1.5-4.6), 19.5 (range 0.9-46.3) and 45.2 (range 2-2052.2), respectively. MTV and MTB were significantly higher in non-epithoeloid tumors compared to other histotype (p=0.022 and 0.03, respectively). For 11C-methionine PET the median percentage of variation before and after talc pleurodesis was 12.8 for SUVmax (%SUV) and 29.9 for MTV (%MTB). Compared to 18F-FDG, the percentage of variation for MTV resulted significantly lower for 11C-methionine (p<0.001), but not for SUVmax. Interestingly, there was an inverse linear correlation between MTV for 18F-FDG at baseline and %SUV or %MTB after pleurodesis (p=0.01), whereas for 11C-methionine only %SUV.

Conclusions: 11C-methionine PET/CT appears able to characterise malignant pleural effusion. This preliminary analyses shows that it might be less influenced by inflammatory reaction related to talc pleurodesis compared to 18F-FDG.

Clinical trial identification: NCT02519049

Legal entity responsible for the study: IRCCS Istituto Clinico Humanitas - Humanitas Mirasole SPA

Disclosure: All authors have declared no conflicts of interest.

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translational research

**Availability of tumour gene expression data facilitates clinical decision-making for patients with advanced cancers**

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**Background:** Whole genome analyses have the potential to identify the full landscape of genomic abnormalities within cancers, and can therefore be used to provide rationales for cancer treatments. The Personalized OncoGenomics study integrates DNA and RNA sequencing information into oncology practice; this analysis evaluates how physicians use the data for clinical decisions and the role of RNA data in identifying actionable targets.

**Methods:** Pts with advanced tumors and a survival > 6 m were eligible. Each had a tumor biopsy and blood sample which underwent comprehensive DNA (N0X) and RNA sequencing followed by bioinformatic analysis including assembly, annotation, and mining of the data to identify somatic aberrations, gene expression changes or other putative cancer “drivers” or actionable targets. Gene expression from tumor RNAseq was compared to the TCGA and Illumina body map. Results were discussed in a multidisciplinary Clinical Genomics Tumour board and characterized as informative, actionable or neither. Clinical actionability can be based on abnormalities of DNA, RNA or both.

**Results:** Between July 2012 and April 2016, 217 pts had complete sequencing data available. Of those, 165 pts had clinically actionable, and 52 had no actionable pathways identified. Of the 165 actionable patients, 355 pending progression, 66 received no POG directed therapy and 71 had POG informed treatment. 60 with no POG directed therapy: 24 poor PS/deceased, 16 clinical trial or off-label treatment not available, 20 POG data was not utilized, 71 treated using POG data: 13 clinical trial, 29 off-label treatment and 29 treatment within guidelines of disease site: 40% of the treatment decisions were based on the RNA information, 45% on a combination of DNA and RNA, and 15% based on DNA alone.

**Conclusions:** Data from DNA abnormalities alone corresponds to the rate noted in panel associated drug matching trials. The availability of RNA expression information greatly increased our ability to identify clinically actionable targets. With the support of the multidisciplinary tumour board meetings and a tiered data system, oncologists had sufficient confidence in the results to seek clinical trials and off-label therapies based on genomic data in the majority of pts.

**Clinical trial identification:** NCT02155621

**Legal entity responsible for the study:** BC Cancer Agency

**Funding:** BC Cancer Foundation


**Lurbinectedin (PM01183) exhibits antitumor activity in PARP-inhibitor resistant germline BRCA PDX and lacks cross-resistance with cisplatin**


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**Background:** PM01183, a trabectedin analogue that inhibits transactivated transcription and induces DNA double-strand breaks, displays remarkable activity in germline BRCA (gBRCA) -related metastatic breast cancer (MBC). However, the mechanisms of primary and acquired resistance to PM01183 and their potential impact on the efficacy of other active agents, namely PARP inhibitors (PARPi) and platinum salts, are unknown. This knowledge may help to delineate the optimal therapeutic sequence to maximize the clinical benefit in the metastatic setting.

**Methods:** We assessed the antitumor activity of PM01183 (0.18mg/kg IV) and cisplatin (6mg/kg IV) qdx5 in a panel of 10 gBRCA PDXs from PM01183-naïve patients (8 PARPi-resistant and 2 PARPi-sensitive), and one additional PDX implanted at PM01183 progression. Additionally, we performed exome sequencing analysis in baseline (pre-treatment, n = 5) and paired tumor biopsies (pre- and post-treatment, n = 5) from patients treated with PM01183.

**Results:** PM01183 exhibited antitumor activity (partial response, complete response or stabilization) in 75% (6/8) of the PARP-resistant PDXs. These results suggest that the mechanisms of resistance to PARPi do not confer resistance to PM01183. Exome sequencing of gBRCA PM01183-resistant tumors unveiled the presence or acquisition of genetic alterations that may disrupt the nucleotide excision repair (NER) pathway in 5 samples, which may impair sensitivity to PM01183. Conversely, these alterations confer sensitivity to cisplatin in vitro and in the clinic. Accordingly, the PDX model implanted at progression to PM01183 showed PM01183 resistance but cisplatin sensitivity. These results suggest that NER alterations potentially driving resistance to PM01183 do not compromise cisplatin efficacy.

**Conclusions:** Our results on cross-resistance in gBRCA MBC suggest that PM01183 is active in the context of PARPi resistance, and that PM01183 resistance will not interfere on platinum efficacy.

**Legal entity responsible for the study:** N/A

**Funding:** PharmaMar S.A.

**Disclosure:** C. Galmarini, P.M. Aviles. Employee at PharmaMar S.A. J. Balnata: Non-commercial research agreement with PharmaMar S.A. All other authors have declared no conflicts of interest.

**Clinical evaluation of the utility of a liquid biopsy (circulating tumoral cells and cDNA) to determine the mutational profile (EGFR, KRAS, ALK, ROS1 and BRAF) in advanced NSCLC patients**

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**Background:** Circulating tumor DNA (cDNA) has emerged as a specific and sensitive blood-based biomarker for detection of several mutations in non–small-cell lung cancer (NSCLC). Other clinical applications include serial monitoring of biomarker status or the development of resistance mutations.

**Methods:** Forty patients with advanced NSCLC who either had a new diagnosis (group 1) or had developed acquired resistance to an EGFR kinase inhibitor (group 2) were analyzed with the highly-sensitive Biocept, Inc Target-SelectorTM Real-Time PCR platform (n = 24) or Next Generation Sequencing (n = 16).

**Results:** Of these, 165 pts had clinically actionable, and 52 had no actionable pathways identified. Of the 165 actionable patients, 355 pending progression, 66 received no POG directed therapy and 71 had POG informed treatment. 60 with no POG directed therapy: 24 poor PS/deceased, 16 clinical trial or off-label treatment not available, 20 POG data was not utilized, 71 treated using POG data: 13 clinical trial, 29 off-label treatment and 29 treatment within guidelines of disease site: 40% of the treatment decisions were based on the RNA information, 45% on a combination of DNA and RNA, and 15% based on DNA alone.

**Conclusions:** Data from DNA abnormalities alone corresponds to the rate noted in panel associated drug matching trials. The availability of RNA expression information greatly increased our ability to identify clinically actionable targets. With the support of the multidisciplinary tumour board meetings and a tiered data system, oncologists had sufficient confidence in the results to seek clinical trials and off-label therapies based on genomic data in the majority of pts.

**Clinical trial identification:** NCT02115621

**Legal entity responsible for the study:** BC Cancer Agency

**Funding:** BC Cancer Foundation

Results: Results showed up to 90% concordance rate of EGFR, KRAS and ALK alterations for the tissue and blood samples. The T790M mutation appeared in 30% of plasma samples analyzed in patients with clinical progression after TKI treatment. Group 1 paired analysis of mutations status monitoring (P< 0.012) showed that the pattern of mutant cDNA and CTCs changed in response to systemic therapy in 83% of the cases (partial response or disease progression; R² = 0.808). cDNA analysis of multiple mutations on group 1 showed: 1) 40% of patients had at least one or more new mutation different than the one detected in tissue biopsy; 2) 28% of EGFR tissue positive patients also had a KRAS mutation; 3) 75% of KRAS positive patients had a BRAF mutation. This technique may be sensitive enough to detect mutations missed by standard tissue genotyping probably due to tissue heterogeneity. Conclusions: Target-Selector™ cDNA and CTC assays appear capable of rapidly detecting EGFR and KRAS mutations as well as ALK rearrangements. It is highly concordant with mutations present in tumor tissue. It would seem to be a viable alternative to identify secondary EGFR mutations such as T790M.

Legal entity responsible for the study: National Cancer Institute. Mexico

Funding: Biocorp, Inc.

Disclosure: L. Barrera, J.R. Borbolla: AstraZeneca full-time employee L. Arnold, J. Poole, Y. Aletidou, B. Gustavson, V. Singh Biocorp, Inc. full-time employee. All other authors have declared no conflicts of interest.

Mouse clinical trials of pancreatic cancer: Integration of PDX models with genomics to improve patient outcomes to chemotherapeutics

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Background: Although a number of treatments are available for pancreatic cancer, these are often administered in prescribed sequences, which may not represent the optimal therapeutic strategy. Technologies enabling multiple regimens to be evaluated simultaneously, identifying beneficial therapy, are needed. Drug screening in patient-derived xenografts (PDXs) is a potential solution. We examined whether pancreatic PDXs capture patient responses to different drugs and report performance metrics highlighting clinical utility.

Methods: Pancreatic tumors from 94 patients were engrafted into immunodeficient mice to generate PDX models. Of these, 19 models were sequenced to identify key genomic alterations with therapeutic implications. Sensitivity to different therapeutics was evaluated and effects on tumor growth aligned to clinical RECIST criteria. A total of 16 PDX screening outcomes were correlated with individual clinical responses and statistical parameters such as sensitivity, specificity, and predictive values calculated.

Results: Of the 94 implanted pancreatic tumors, 82 have completed the implantation process, with 72 (88%) successfully engrafting. Sequencing revealed mutations in 451 common genes, including those informing treatment choices such as EGFR, KRAS, and BRCA1/2. PDX models from 39 patients were screened in 144 drug tests employing 56 FDA-approved agents and 9 experimental agents. In 14/16 (88%) cases with available data, a correlation between clinical and PDX outcomes was noted and from this cohort we calculated positive and negative predictive values of 82% and 100% respectively.

Conclusions: Using a small cohort, we showed drug responses in pancreatic PDX model correlate with clinical outcomes to the same therapy. Application of such models to guide treatment decisions for pancreatic cancer patients may help lead to better outcomes. Moreover, given the clinical relevance of these models, they could also be deployed as real-time patient surrogates during drug development and clinical trials, permitting real-time analysis of treatment responses and identification of biomarkers that predict different therapeutic outcomes.

Legal entity responsible for the study: N/A

Funding: Champions Oncology

Disclosure: A. Davies, D. Camadina. Employee of Champions Oncology Stockholder in Champions Oncology M. Hidalgo, J. Stebbing: Advisory board for Champions Oncology A. Katz: Employee of Champions Oncology Stockholder of Champions Oncology D. Sidransky: Chairman of Board for Champions Oncology Stockholder in Champions Oncology

Generation and characterization of a collection of patient-derived xenografts (PDXs) models for translational lung cancer research

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Background: The use of preclinical models is essential in translational cancer research. An appropriate preclinical model must be useful for drug screening, biomarker discovery and preclinical evaluation of precision therapeutic strategies. Conventional available preclinical models are not optimal to this end. Xenografts from cell lines do not reconstitute the architecture and environment of human cancer and acquire mutations not found in the original tumor. Our aim is to generate and characterize a collection of PDX models for translational lung cancer research by implantation of lung primary human tumors in mice. Mainly, this collection will be used for biomarker identification and preclinical evaluation of new therapeutic strategies targeted to bad prognostic lung tumors with suboptimal therapeutic approaches.

Methods: Resected NSCLC from patients were subcutaneously xenografted and expanded in successive groups of nude mice to get a perpetual live bank of each tumor. Every tumor, which successfully grew in mice, was used to analyze the genome and transcriptome by NGS techniques. Furthermore, a bank of frozen pieces of tumor was stored in order to generate later cohorts of tumor-bearing mice suitable for preclinical drug evaluation and biomarker identification.

Results: We have characterized 32 different PDX models at the genomic and transcriptomic level: 20 SCC, 10 ADC and 2 LCC. The PDX models mostly retain the primary histologic and molecular characteristics of their donors and recapitulate the heterogeneity of human lung cancer models. In our PDX collection we have sufficiently represented all the NSCLC histology and the most relevant molecular alterations in lung cancer in order to perform precision medicine evaluation studies.

Conclusions: We have generated and characterized a collection of PDX models of NSCLC, which represents the most frequent histological and molecular subtypes of this
type of LC. This collection will be readily useful to integrate drug screening with biomarker discovery and to evaluate precision therapeutic strategies preclinically. Our future aim will be to use this collection in order to identify new effective therapeutic strategies targeted to bad prognostic subtypes of lung cancer.

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Disclosure: All authors have declared no conflicts of interest.

Prevalence and clinical associations of PTEN loss in non-small cell lung carcinoma (NSCLC) patients (pts) of the European Thoracic Oncologic Platform (ETOP) Lungscape cohort

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Background: MEK inhibition is interesting but still has modest efficacy in KRASm LAC patients. STAT3 activation and AXL mediated epithelial-to-mesenchymal transition cause resistance to MEK inhibition. p21-activated kinase 1 (PAK1) regulates ERK activation and its role in KRASm LAC warrants further investigation. YAP1 expression increases tametinib efficacy in KRASm LAC cells. We have explored the role of STAT3, AXL, PAK1 and YAP1 in KRASm LAC cells and developed a rationale for combinatorial strategies.

Methods: Quantitative real-time PCR gene expression analysis was performed in 4 KRASm LAC cell lines (H25, A549, H460 and Calu-3). The MEK inhibitor (i) selumetinib was combined with evodiamine (STA3), R428 (AXL) or ivermectin (dual YAP1-PAK1i). Cell viability was assessed by the thiazolyl blue assay and the combination index (CI) was calculated for the analysis of drug interactions.

Results: We first evaluated the effect of selumetinib in the 4 KRASm LAC cell lines. H23 and H460 were less sensitive to selumetinib than A549 and Calu-3. Among the cell lines examined, H23 cells had the highest STAT3 mRNA expression and the combination of selumetinib with evodiamine synergistically suppressed cell viability (CI < 0.8). The combination of R428 with selumetinib was also synergistic in H23 cells (CI < 0.58) that have moderate AXL mRNA expression. High PAK1 mRNA expression was detected in the A549 selumetinib-sensitive cell line, and the addition of the dual PAK1-PAK1i, ivermectin to selumetinib increased the effect of MEK inhibition alone (CI = 0.17). To our surprise, the combination of ivermectin with selumetinib was not synergistic in the H23 cells that overexpress YAP1. H460 and Calu-3 cells have moderate or low STAT3, AXL and PAK1 expression. Further cell viability experiments as well as immunoblotting and biomarkers analysis in clinical tumor samples are ongoing.

Conclusions: The heterogeneous biology of KRASm LAC may partially explain the difficulties encountered in the development of efficient therapies. Our data, until now, identify STAT3, AXL and PAK1 as potential biomarkers and the targeting of them as a potential synergistic strategy to combine with MEK inhibition.

Legal entity responsible for the study: N/A.

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Disclosure: All authors have declared no conflicts of interest.

Differential expression profile of lung squamous cell carcinoma (LSCC) and druggable targets to be combined with nectinibumab (N)

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Background: LSCC lacks effective targeted therapies. EGFR is commonly expressed in LSCC and N, an anti-EGFR monoclonal antibody (mAb), is the only approved targeted therapy that with chemotherapy provides a small (clinically irrelevant) survival benefit as 1st-line treatment in metastatic LSCC. AXL, STAT3 or YAP1 pathway activation, diminishing the efficacy of anti-EGFR mAbs. Herein, we evaluate the relevance of these strategies targeted to bad prognostic subtypes of lung cancer. Our future aim will be to use this collection in order to identify new effective therapeutic strategies targeted to bad prognostic subtypes of lung cancer. The MEK inhibitor (i) selumetinib was combined with evodiamine (STA3), R428 (AXL) or ivermectin (dual YAP1-PAK1i). Cell viability was assessed by the thiazolyl blue assay and the combination index (CI) was calculated for the analysis of drug interactions.

Methods: We first evaluated the effect of selumetinib in the 4 KRASm LAC cell lines. H23 and H460 were less sensitive to selumetinib than A549 and Calu-3. Among the cell lines examined, H23 cells had the highest STAT3 mRNA expression and the combination of selumetinib with evodiamine synergistically suppressed cell viability (CI < 0.8). The combination of R428 with selumetinib was also synergistic in H23 cells (CI < 0.58) that have moderate AXL mRNA expression. High PAK1 mRNA expression was detected in the A549 selumetinib-sensitive cell line, and the addition of the dual PAK1-PAK1i, ivermectin to selumetinib increased the effect of MEK inhibition alone (CI = 0.17). To our surprise, the combination of ivermectin with selumetinib was not synergistic in the H23 cells that overexpress YAP1. H460 and Calu-3 cells have moderate or low STAT3, AXL and PAK1 expression. Further cell viability experiments as well as immunoblotting and biomarkers analysis in clinical tumor samples are ongoing.

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Legal entity responsible for the study: N/A.

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Repeated exposure to cisplatin enhances NK cell-mediated cytotoxicity via up-regulation of NKG2D ligands in non-small cell lung cancer cells

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Background: Cisplatin (CDDP) is one of the key drugs for non-small cell lung cancer (NSCLC) and CDDP-resistant mechanisms have been investigated, while the role of immune cells on excluding CDDP-treated cancer cells is poorly understood. Here we demonstrate repeated exposure to CDDP enhances NK group 2 member D (NKG2D) ligands MHC class I-related chain A and B (MICA/B) and UL16 binding protein (ULBP)-2/5/6 in NSCLC cell lines while attenuates them in tumor tissue from patients with NSCLC.

Methods: A49 cells were exposed to 10 µM of CDDP (A49-CR) at least thrice then expressions of NKG2D ligands in tissue samples from NSCLC patients who received cisplatin (dual YAP1-PAK1i) or GANT61 and mebendazole (GLIi) alone or in combination. Western blotting analysis, as well as further cell viability experiments with drugs alone and in combination with CDDP, are ongoing.

Conclusions: LSCC is a heterogeneous disease, in which common signaling pathways dictate distinct pathologic outcomes. The awareness of these differences is necessary while planning efficient strategies to improve the scant clinical benefit with EGRF mAbs.

Legal entity responsible for the study: N/A

Disclosure: All authors have declared no conflicts of interest.

Serum microRNAs as potential biomarkers for lung cancer

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Background: MicroRNAs are single-stranded RNA species that constitute a class of non-coding RNAs, and are emerging as key regulators of gene expression. Since each miRNA is capable of regulating multiple genes, miRNAs are attractive markers for studies of coordinated gene expression. The interest in circulating RNAs as biomarkers is rapidly increasing as their potential is being realized. In this study, we investigated serum miRNA expression to compare non-small-cell lung cancer patients and controls by our previous studied serum miRNA profiles.

Methods: This study involved RNA isolation from 184 sera specimens including those from lung cancer patients and age- and gender-matched controls (n = 92 each). Serum RNA was isolated with miRNeasy Serum/Plasma Kit (Qiagen), and reverse transcription was performed using the miScript II RT kit (Qiagen) according to the manufacturer’s instructions. The data were analyzed using the PCR array data analysis tools (Qiagen). Appropriate informed consent was obtained from the participating patients, and those who agreed to participate.

Results: Differences in miRNA profile identified support circulating miRNAs as potential clinical relevance of these miRNAs as minimally invasive biomarkers for lung cancer. More extensive studies of lung cancer and control serum specimens are warranted to independently validate the potential clinical relevance of these miRNAs as minimally invasive biomarkers for lung cancer.

Legal entity responsible for the study: N/A

Disclosure: All authors have declared no conflicts of interest.
Background: Nivolumab, an anti PD-1 inhibitor, has been approved for the treatment of previously treated advanced or metastatic non-small-cell lung cancer (NSCLC). The response rate is about 20% with nivolumab. The inter-patient variability in clinical outcomes to nivolumab is large and could be influenced by its pharmacokinetics. However, no data is currently available about the inter-patient variability in plasma exposure to nivolumab in NSCLC outpatients. The aim was to investigate the inter-patient variability in plasma level of nivolumab from 27 NSCLC outpatients.

Methods: NSCLC patients were treated with nivolumab (3 mg/kg) every two weeks. Blood samples were collected just before the infusion on days 0 (baseline), 14, 28 and 42 after treatment start. Plasma trough levels (Cmin) of nivolumab were assayed with home-made ELISA. Univariate linear regression models were performed in order to explain the inter-patient variability in nivolumab Cmin on day 42. Multivariate model included all variables which were significant at the 10% level in the univariate analyses.

Results: The calibration for nivolumab assay was linear in the range 5-100 µg/mL. Intra- and interday imprecision for three internal quality controls (5, 20 and 75 µg/mL) were less than 9 and 12%, respectively. The median age of the cohort was 68 years (range 41-84) and the sex ratio (female/male) 1:2.7. The median dose of nivolumab was 207 mg (range 147-288). No nivolumab was detected in baseline samples. The mean nivolumab Cmin was 17.3 ± 4.8 µg/mL (CV = 27.8%), 25.0 ± 9.7 µg/mL (CV = 38.8%) and 33.0 ± 12.9 µg/mL (CV = 39.1%) on days 14, 28 and 42, respectively. A significant variation in nivolumab Cmin was observed over the time (one-way Anova test, p < 0.001). In the multivariate linear regression analysis, nivolumab Cmin on day 42 was independently associated with igg level (β = -3.25; p = 0.0022) and ALAT (β = 0.45; p = 0.042).

Conclusions: These preliminary results highlight a large inter-patient variability in nivolumab Cmin in NSCLC outpatients. Further PK/PD investigations are warranted to identify the influence of this pharmacokinetic variability on clinical outcomes.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.
Results: Expression of miR-34a target genes was repressed in bWBCs 24 hrs after the start of MRX34 dosing. The effect was dose-dependent such that the depth of repression increased at higher MRX4 doses corresponding to increased exposure to and uptake of miR-34a in bWBCs. In contrast, expression of p21 (CDKN1A), a tumor-suppressor gene specifically induced by miR-34a, was increased.

Conclusions: This qRT-PCR analysis of bWBC samples obtained from patients treated with MRX34 in a first-in-human clinical trial of miRNA cancer therapy showed dose-dependent modulation of expression in target genes directly regulated by miR-34a. Our work suggests that MRX34 effectively delivers active miR-34a mimics to bWBCs in pts with cancer, and provides a potentially useful method to evaluate biomarkers of response to MRX34 therapy.

Clinical trial identification: NCT01839971

Legal entity responsible for the study: Mirna Therapeutics Inc


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**153SP**

circular RNA: A novel regulatory non-coding RNA expressed in prostate cancer

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Background: Recent advances in prostate cancer (PCA) have led to the development of new treatments that target the androgen receptor (AR) pathway. However, some pts present with intrinsic resistance to treatment while others eventually develop acquired resistance. The mechanisms associated with the development of resistance have yet to be fully characterized. Non-coding RNAs (ncRNA) are RNA molecules, which are not translated into protein and include microRNAs (miRNA). Recently a novel type of ncRNA was identified and termed circular RNA (circRNA). circRNA appear to play a crucial role in gene expression through the regulation of miRNAs. The aim of this study is to determine the role of circRNA in enzalutamide resistance and their interaction with miRNAs associated with PCA.

Methods: circRNA was extracted from a panel of prostate cell lines, which included benign (n = 3), malignant (n = 5) and an isogenic model of enzalutamide resistance. circRNA profiling was performed using an Arraystar microarray platform. Differentially expressed circRNAs were ranked according to fold change between groups (FC >2; p-value < 0.05). Additionally, circRNA/miRNA interactions were predicted based on sequence pairing identified by TargetScan and verified by miRanda.

Results: In total 9,757 circRNAs were classified as present across the panel of cell lines. The majority of circRNA were downregulated in enzalutamide resistant cell lines compared to the sensitive cell lines (p = 0.003). In addition, 651 circRNA/miRNA interactions were identified allowing identification of circRNA/miRNA interactions relevant to PCA. Predicted miRNA targets were determined for circRNAs with FC greater than 2. For each circRNA up and downregulated, 5 binding sites for their targeted miRNAs were identified.

Conclusions: circRNA/miRNA interactions were predicted based on sequence pairing identified by TargetScan and verified by miRanda. Identified circRNA/miRNA interactions may provide potential biomarkers of response to enzalutamide and be relevant to PCA.

Legal entity responsible for the study: IOCRG

Disclosure: All authors have declared no conflicts of interest.

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**153EP**

Description and prognostic value of the mutational load across various metastatic solid tumors in the prospective MOSCATO-01 and MATCH-R trials

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Background: MOSCATO-01 and MATCH-R are ongoing prospective precision medicine trials (NCT0166019 and NCT0121792). They allow genomic analysis of purposefully acquired tumor biopsies obtained in patients with various types of metastatic solid tumors. MATCH-R encompassed whole exome sequencing (WES) since its inception, while MOSCATO incorporated WES in 2015.

Methods: To describe the landscape and evaluate the prognostic impact of the mutational load in metastatic solid tumors blinded from histology and history of previous treatment, whole exome sequencing was performed on prospective samples with both high tumor cellularity (> 30%) and good DNA.

Results: Mutational load from 160 patients was obtained, with 9 patients having multiple longitudinal mutational loads and 4 patients with synchronous mutational loads from different biopsy sites. Mutational loads in HER2-positive tumors ranged from 0.2 to 28.7 mut/Mb with 80% of patients under 5 mut/Mb. In this heterogeneous population with various preceding therapies, mutational load was not associated with overall survival. Median follow-up was 46 months (95% CI: 36-57).

Conclusions: Prospective evaluation of the mutational load is routine feasible in precision medicine trials. Results were obtained within 4 weeks of tumor biopsy. In this heterogeneous population, mutational load is not prognostic. Signatures of mutational processes and neoantigens are currently being characterized in our patients.

Legal entity responsible for the study: None

Disclosure: All authors have declared no conflicts of interest.

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**136P**

The role of PP2A in innate resistance to HER2-targeted therapy

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Background: We previously identified protein phosphatase 2A (PP2A) as a potential mediator of resistance to lapatinib in cell line models of acquired lapatinib resistance (McDermott, 2014). The aim of this study was to evaluate the potential role of PP2A in innate resistance to lapatinib and trastuzumab.

Methods: Parallel proliferative assays were carried out to assess sensitivity to lapatinib, trastuzumab and the PP2A inhibitors, okadaic acid and LB-100, alone and in combination with lapatinib, using an acid phosphatase assay. Immunoblotting for eEF2, p-eEF2, PPP2CA, p-PPP2CA, Akt, p-Akt, ERK, p-ERK, S6K and p-S6K was performed.

Results: Cell lines that are intrinsically resistant to lapatinib and/or trastuzumab were significantly more sensitive to okadaic acid (p = 0.020, p < 0.001). In three of the four intrinsically resistant cell lines, treatment with okadaic acid restored sensitivity to lapatinib.

Conclusions: pp2a inactivation may play a role in innate resistance to lapatinib and/or trastuzumab.

Legal entity responsible for the study: Dublin City University

Disclosure: J. Crown. Research funding from Roche, GSK, Boehringer Ingelheim, Eisai and advisory/consulting role for Novartis, Eisai, Pfizer, Genomic Health, Teva, New Oncology and Bayer. N. O’Donovan: Research funding from Eisai, Boehringer Ingelheim and GSK. All other authors have declared no conflicts of interest.
Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as predictive biomarkers of pathologic complete response (pCR) in neoadjuvant breast cancer: an Irish Clinical Oncology Group study (ICORG 16-20)

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Background: Over the past few years, the rapidly advancing field of cancer immunology has provided solid evidence that the systemic inflammatory response, usually measured by surrogate blood-based parameters, such as neutrophil or platelet count, has an important role in the progression of several solid tumors. In this study, we investigate the association between pre-neoadjuvant therapy NLR and PLR, and pCR in breast cancer

Methods: We performed a retrospective review of patients with non-metastatic breast cancer treated with neoadjuvant therapy followed by surgery in seven cancer centers across Ireland. Blood cell counts were obtained within one week before the start of neoadjuvant therapy. The NLR and PLR were defined as the absolute neutrophil count and the absolute platelet count, respectively, divided by the absolute lymphocyte count. We determined cutoff values of 2.05 and 138.19 for the NLR and PLR respectively, to be optimal to discriminate between high and low groups. In the non-pCR group, 68.4% (n = 142) had a NLR ≥ 2.05 compared to 44.7% (n = 38) in the pCR group. Patients with high NLR were less likely to achieve pCR compared to patients with low NLR (p = .006, OR: 1.72, 95% CI: 1.03 to 2.86 ). In the non-pCR group, 58.9% (n = 129) had a PLR ≥ 138.19 compared to 44.7% (n = 38) in the pCR group. Patients with high PLR were less likely to achieve pCR compared to those with low PLR (p = .026, OR: 1.72, 95% CI: 1.03 to 2.86 ). In the non-pCR group, 58.9% (n = 129) had a PLR ≥ 138.19 compared to 44.7% (n = 38) in the pCR group. Patients with high PLR were less likely to achieve pCR compared to those with low PLR (p = .036, OR = 1.72, 95% CI: 1.03 to 2.86 ). In the non-pCR group, 58.9% (n = 129) had a PLR ≥ 138.19 compared to 44.7% (n = 38) in the pCR group. Patients with high PLR were less likely to achieve pCR compared to those with low PLR (p = .036, OR = 1.72, 95% CI: 1.03 to 2.86 ).

Conclusions: High NLR and PLR are independently associated with poor response to neoadjuvant therapy in breast cancer

Clinical trial identification: ICORG 16-20

Legal entity responsible for the study: Irish Clinical Oncology Research Group (ICORG 16-20)

Funding: Irish Clinical Oncology Research Group (ICORG 16-20)

Disclosure: All authors have declared no conflicts of interest.

Androgen receptor and estrogen receptor beta interplay in triple negative breast carcinomas

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Background: Triple negative breast cancer (TNBC) is an aggressive breast cancer subtype. We explored the role of androgen receptor (AR) in TNBC focusing on its association with ERβ in ligand-independent AR activation.

Methods: We performed in vitro experiments in breast cancer cell lines BT-20 and MDA MB 453, which express high and low levels of AR, respectively. We have also studied PI3K/AKT pathway molecules mTOR, PTEN and AKT with immunoblot analysis and RT-PCR. Immunoblot analysis of BT-20 and MDA MB 453 cells for ERβ revealed a specific interaction between ERβ and AR, indicating the strong proliferative effect of AR in TNBC. The cellular model which expresses both AR and ERβ showed that ERβ modulates AR proliferative activity by increasing PTEN and reducing activation of downstream molecules of PI3K/AKT pathway. Agonists of both receptors (testosterone and 17β-estradiol for AR and ERβ, respectively) enhanced receptors expression, affecting the expression levels of the PI3K/AKT signaling pathway molecules. Treatment with the AR antagonist bicalutamide did not have significant impact. Using IP, a specific interaction between ERβ and AR was revealed.

Conclusions: There is strong evidence that ERβ is involved in TNBC progression. Our data provide a strong anti-proliferative effect of ERβ in TNBC cells via the PI3K/AKT signaling pathway and may represent a significant therapeutic target. More detailed studies are ongoing to this concept, which may have considerable impact for the treatment of TNBC patients.

Legal entity responsible for the study: N/A

Funding: Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Disclosure: All authors have declared no conflicts of interest.

Presence of tumor-specific cytolytic T cells in human primary breast carcinomas: consequences for immunotherapy

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Background: Immunotherapy through stimulatory antibodies targeting the CTLA-4 or PD-1 pathways has demonstrated clinical efficacy in a fraction of patients with various cancers. It is likely that the main immune effectors of these therapies are CD8+ cytolytic T lymphocytes (CTL) recognizing tumor-specific antigens. Highly antigenic tumors such as metastatic melanomas are often immunogenic, i.e. they stimulate spontaneous anti-tumor CTL responses. This immunogenicity, of which the presence

compromises the efficiency of a particular drug expected to target the detected somatic mutations. In so called “Umbrella” trials a set of preselected drugs are tested in cancer patients with different cancer types with distinct mutations. Despite of promising results of different studies based on molecular testing, the impact of comprehensive screening approaches is still underestimated. In a personalized medicine the molecular tumor analyses has to complement other diagnostics and enable up-to-date therapy such as targeted therapies, immunotherapies, and others.

Methods: We compared a dataset of 25 breast cancer cases who had previously undergone CeGaT somatic tumor panel (NGS-based panel diagnostics comprising 649 tumor-related genes) or tumor exome diagnostics. All cases were discussed in an interdisciplinary tumor board composed by gynecologists, oncologists, clinical and molecular geneticists. Among others, issues such as clinical relevance of the molecular report in the context of the individual clinical setting were discussed retrospectively.

Results: In an adjuvant setting, standard/guideline therapies were considered the best approach. In locally advanced tumors, relapse or metastatic disease, the molecular report was considered extremely relevant, either consistent with clinical decisions or enabling new approaches, including targeted or immunologic therapies, but also selected chemotherapy. Only in 1/25 cases (4 %), no therapeutically relevant somatic mutation could be detected. We present select examples of cases, in which the therapeutic approach would be re-considered retrospectively.

Conclusions: The retrospective evaluation resulted in the implementation of a monthly interdisciplinary molecular tumor board discussing current patients and prospective approaches. All patients with locally advanced tumors, relapse or metastases are offered comprehensive molecular testing and comprehensive individual evaluation of therapeutic approaches.

Legal entity responsible for the study: none

Funding: CeGaT GmbH

Disclosure: S. Armeau-Ebinger, D. Döcker, C. Kyrizakos, M. Menzel, A. Rinklb. Employed at CeGaT GmbH, which provides molecular tumor diagnostics. All other authors have declared no conflicts of interest.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as predictive biomarkers of pathologic complete response (pCR) in neoadjuvant breast cancer: an Irish Clinical Oncology Group study (ICORG 16-20)
of tumor-infiltrating T cells (TILs) is probably a surrogate marker, might be a predictive marker for clinical benefit to immunostimulatory antibodies. The immunogenicity of primary breast carcinomas for CD8+ T cells has not been studied, but the amounts of TILs have been positively correlated with patients’ survival. Here we wished to obtain evidence for the presence of tumor-specific CD8+ T cells in TILs from primary breast carcinomas.

Methods: From 5 tumors (2 ER+/HER2-, 2 ER-/HER2+, 1 ER+/HER2-) we isolated TILs and derived a random set of ±100 CD8+ T cell clones that we screened for recognition of candidate tumor-specific antigenic peptides selected through tumor exome sequencing and gene expression profiling. These peptides were encoded either by mutated genes or by cancer-germline genes.

Results: For 4 tumors, we screened 61-142 T cell clonotypes for recognition of 23-61 candidate mutated peptides, without any positive result. For the last tumor (ER+/HER2-), 6 out of 57 T cell clonotypes recognized 4 out of 109 candidate mutated peptides but not the corresponding wild-type peptides. This tumor contained more mutations than the other line, and displayed microsatellite instability.

Conclusions: Some human primary breast carcinomas are immunogenic, as one tumor contained at least 10% of tumor-specific cells among the CD8+ TILs. Our observation corroborates the association between high mutation burden and CTL response of mutated tumor antigens. The presence of tumor-specific CD8+ T cells suggests that the corresponding patient could benefit from the currently used immunostimulatory antibody.

Clinical trial identification: code No.002008-01 - non interventional trial
Legal entity responsible for the study: Cliniques Universitaires Saint Luc
Funding: Cliniques Universitaires Saint Luc, Belgian Cancer Foundation, Fonds de la Recherche Scientifique
Disclosure: All authors have declared no conflicts of interest.
Results: Both drugs were found active in suppressing growth of a panel of TNBC cell lines as well as of CSC cell line in vitro, which correlates with their ability to suppress Wnt signal transduction. As expected, these drugs suppress proliferation as well as migration of the cancer cells – two processes that are governed by Wnt signaling. We have also investigated if these compounds could be used as the co-treatments by calculating their combination index. A similar trend was obtained in vivo, where suramin and clofazimine were able to suppress growth of the tumor xenografts without inducing significant overt side effects. Our data however presumes that suramin unlike clofazimine must be used at the doses significantly higher than those used for its intended purpose.

Conclusions: This work is an attempt to translate our previous investigations on the molecular mechanisms of the clofazimine and suramin action in Wnt pathway in vitro and bring these advances to the level of clinics. Our results show that their anti-Wnt activity results in the ability to suppress TNBC growth in vivo with few or no side effects visible in xenografted animals. Challenges remain however to establish optimized regimen for their new application in order to maximize their efficacy and to perform trials with their usage as a co-therapy.

Legal entity responsible for the study: University of Lausanne

Funding: Swiss National Science Foundation - SNF

Disclosure: All authors have declared no conflicts of interest.

1546P

The number of tumorspheres cultured from CETCs in breast cancer patients is directly related to stage of disease and administration of chemotherapy

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Background: Breast cancer is one of the leading causes of cancer death for women worldwide. Major hurdles for a successful treatment are cancer metastasis, resistance to therapy and disease recurrence. The presence of CETCs is closely related to metastasis formation, but the mechanisms through which CETCs promote recurrence of disease are still unclear. Therefore, the aim of this study was to determine the proliferative capacity of CETCs by analyzing the frequency of tumoursphere formation with subsequent phenotypic characterization of the spheres arising in breast cancer patients.

Methods: CETCs were cultured under conditions favoring growth of tumourspheres from patients with breast cancer, including a subpopulation of 23 metastatic disease. Cell viability, stem cell marker expression and ALDH1 activity was evaluated by fluorescence scanning microscope (Olympus ScanR).

Results: Sphere formation was observed in 79% of patients with breast cancer. In the current study we found that the number of tumorspheres depended on stage of disease. Patients in stage IV had statistically significant more tumourspheres compared to patients in stage I (median 6 vs. ~0.002). The most important factor for growing tumourspheres was chemotherapy. Patients with chemotherapy treatment had lower numbers of tumourspheres compared to patients without chemotherapy (median 2 vs. 5 ~0.002). Interestingly, patients with HER2 positive primary tumour had higher number of tumourspheres with median 10. Analysis of surface marker expression profile of tumourspheres showed that spheres cultured from CETCs had typical phenotype of cancer stem cells with a high enzymatic activity for ALDH1. There was no sphere formation in a control group with 50 healthy donors.

Conclusions: This study demonstrates that a small fraction of CETCs has proliferative activity. Identifying the CETC subset with cancer stem cell properties may provide a suitable model for tumoursphere formation, but the mechanisms through which CETCs promote recurrence of disease are still unclear. Therefore, the aim of this study was to determine the proliferative capacity of CETCs by analyzing the frequency of tumoursphere formation with subsequent phenotypic characterization of the spheres arising in breast cancer patients.

Legal entity responsible for the study: University of Lausanne

Funding: Swiss National Science Foundation - SNF

Disclosure: All authors have declared no conflicts of interest.

1547P

Germline and somatic multi-gene sequencing in patients (pts) with advanced high grade serous ovarian cancer (HGSOC) and triple negative breast cancer (TNBC)

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Background: Genomic similarities of HGSOC and TNBC include germline pathogenic variants (GPV) in BRCA1/2 and somatic mutations in homologous recombination (HR) genes. Non-BRCA GPV in HGSOC and TNBC pts have also been identified through multi-gene Next Generation Sequencing (NGS). Somatic multi-gene analysis can identify pts with acquired HR mutations for trials with novel targeted drugs, like PARP inhibitors.

Methods: Study cohort included HGSOC and TNBC pts unscheduled for family history or age at diagnosis, enrolled in an institutional molecular screening program (NCT01505400). DNA extracted from matched blood and tumor samples (FFPE) was additionally tested using a lab-developed NGS Hereditary Cancer Panel of 52 cancer predisposition genes, including 11 HR genes. Medical records were reviewed for clinical course, pathology and prior germline testing results. All pts consented for research on banked samples and return of GPV by a genetic counsellor.

Results: Of 58 analyzed pts (48 %, 8/17 TNBC and 40/41 HGSOC) had prior germline testing, which revealed GPV in 17 pts (BRCA1 (12 pts), BRCA2 (4 pts) and PALB2 (1 pt). We identified previously unknown GPV in five pts (9%, see table) and a potentially clinically relevant RAD51 variant in a previously known germline BRCA1 carrier with HGSOC.

Table: 1547P

<table>
<thead>
<tr>
<th>Pt</th>
<th>Cohort</th>
<th>New GPV</th>
<th>Prior germline testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TNBC</td>
<td>BRCA2</td>
<td>Patient declined</td>
</tr>
<tr>
<td>2</td>
<td>TNBC</td>
<td>BRCA1 + CHEK2</td>
<td>Provincial testing criteria not met</td>
</tr>
<tr>
<td>3</td>
<td>HGSOC</td>
<td>CHEK2</td>
<td>BRCA1/2 wild type (WT)</td>
</tr>
<tr>
<td>4</td>
<td>HGSOC</td>
<td>PALB2</td>
<td>BRCA1/2 WT</td>
</tr>
<tr>
<td>5</td>
<td>HGSOC</td>
<td>FANC1</td>
<td>BRCA1/2 WT</td>
</tr>
</tbody>
</table>

Among 22 GPV carriers, three HGSOC pts (14%) also had somatic mutations in HR genes (BRCA1, FANGD2), in addition to their GPV that were present in the tumor. Of 36 germline WT pts, five HGSOC pts (14%) and four TNBC pts (10%) had somatic mutations in HR genes (BRCA1/2, FANC) including one who achieved a partial response on a clinical trial with a PARP inhibitor.

Conclusions: Comprehensive germline and tumor analysis with 52 gene panel in advanced HGSOC and TNBC found previously unidentified GPV in 9% of pts and somatic mutations in HR genes in 14% of germline WT pts. This increases options for targeted therapeutics with investigational agents, such as PARP inhibitors.

Legal entity responsible for the study: Princess Margaret Cancer Centre

Funding: AstraZeneca

Disclosure: All authors have declared no conflicts of interest.
Response to savolitinib (AZD6094/HMPL-504, a potent and selective MET inhibitor) in a papillary renal cell carcinoma patient harbouring a novel MET activating mutation

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Background: Metastatic renal cell carcinoma (M-RCC) is a highly lethal disease. MET (c-Met) is a potent growth factor receptor that is activated in many cancers. MET promotes proliferation, survival and tumour invasion and is overexpressed in several cancer types. MET inhibitors including savolitinib (AZD6094/HMPL-504) are currently in clinical trials. MET inhibitors have been approved for patients with a specific MET mutation; however, there is no predictive testing.

Methods: This case study describes a 56 year old woman who was enrolled in a Phase II trial of savolitinib in patients with M-RCC (NCT02127710) in September 2014. A diagnostic sample was collected from the patient in December 2012 during resections of several metastatic lesions to the abdominal lymph nodes. This archival tumor sample was analyzed by central immunohistochemistry. Additionally, NGS analysis of circulating tumor DNA (ctDNA) isolated from plasma can be used to test for the presence of driver mutations in patients with metastatic renal cell carcinoma. The primary post hoc objective of this study was to evaluate the efficacy of savolitinib in unaffected standard of care M-RCC patients.

Results: The clinicopathologic details of the patient were as follows: a 56 year old female with a recent diagnosis of M-RCC to the liver, lung, and bone with a background of hypertension. Savolitinib was started at a dose of 150 mg and treatment was continued for 25 weeks. Response evaluations were performed every 8 weeks. The patient had a partial response (PR) of the right adrenal gland. There was no disease progression (PD) and no treatment-related adverse events (AEs).

Conclusions: To our knowledge, this is the first case report of a patient with a novel MET activating mutation exhibiting a clinical response to a MET inhibitor. Interestingly, the MET activating mutation was not detected on the diagnostic tumor sample which highlights the potential role of ctDNA analysis as an additional tumour genotyping tool.

Disclosure: All authors have declared no conflicts of interest.

Response to savolitinib (AZD6094/HMPL-504, a potent and selective MET inhibitor) in a papillary renal cell carcinoma patient harbouring a novel MET activating mutation

Method: Next Generation Sequencing (NGS) of the diagnostic tumor sample (Foundation Medicine Inc, Cambridge, MA, USA) with a median exon coverage of 50x demonstrated the existence of a MET mutation MET_c.5398C > T with an allele fraction of 24%.

Results: The amino acid substitution of L1195F is located in exon 18 within the kinase domain of the MET receptor tyrosine kinase and has been previously reported in papillary renal cell carcinoma patients (Schmidt et al Nature Genetics 1997, Albulescu et al CCR 2014). We demonstrate for the first time that this MET L1195F mutant is actionable. MET L1195F is predicted as an activating mutation (PolyPhen and SIFT) and is phosphorylated in vitro when overexpressed demonstrating the activation of MET. The MET L1195F mutant is demonstrated to be sensitive to savolitinib, a selective and potent MET inhibitor.

Conclusions: Although MET L1195F confers tumor control and benefit from savolitinib, after 36 weeks of treatment and 29.7% best tumor shrinkage from the baseline tumor embarrassment, the patient in which we found this mutation unfortunately relapsed and died shortly after. Future samples were collected from this subject prior to treatment, during the course of savolitinib treatment and upon relapse. NGS analysis of circulating tumor DNA (ctDNA) isolated from plasma can be used to monitor for emerging receptor mutations. Characterization of the mechanisms of resistance to savolitinib will provide rationale for the management of such patients going forward.

Disclosure: M.M. Frigault, D. Stetson, E. Maloney, E. Barry, B. Dougherty, J.C. Barrett, C. D’Cruz: Employed by AstraZeneca. All other authors have declared no conflicts of interest.

Legal entity responsible for the study: AstraZeneca PLC

Funding: AstraZeneca PLC

Investigating the combination of bevacizumab and the EGF receptor inhibitor erlotinib for the treatment of metastatic renal cell carcinoma

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Background: One of the major characteristics of metastatic clear cell renal cell carcinoma (mRCC) is the over-expression of the Vascular Endothelial Growth Factor (VEGF). Several treatments against this pro-angiogenic factor are usually used such as sunitinib or the anti-VEGF bevacizumab (BVZ). In a mouse experimental model of RCC we have described that BVZ accelerated tumor growth. A down-regulation of phospho tyrosine phosphatase receptor kappa (PTPRK) by tumor cells under the selection pressure exerted during BVZ treatment is a potential explanation for this accelerated growth. The main target of PTPRK is the Epidermal Growth Factor Receptor (EGFR). Thus, down-regulation of PTPRK leads to a constitutive activation of the EGFR. According to the literature BVZ combined with ERLO does not benefit patients. However, the EGFR mutations were not checked in this clinical study. Considering these data, a combination of an inhibitor of EGFR (erlotinib/Tarceva) with the BVZ/interferon alpha (INF) treatment could be more efficient against RCC growth.

Methods: Tumor cells were injected subcutaneously, bioluminescence was quantified with an in vivo imaging system. 1550P

Results: The BVZ/INF/ERLO treatment strongly reduced tumor volume and no tumor relapse has been observed compared to the reference treatment sunitinib. The triple combination reduces the production of redundant pro-angiogenic/pro-inflammatory cytokines of the IL-1R+CXCL family and induces a polarization of macrophages towards the M1 phenotype. The number of lymphatic vessels is inferior in tumors receiving this combination compared to the tumors of BVZ/INF or ERLO treated mice. Although no study has shown that BVZ combined with ERLO does not benefit patients, the EGFR mutations were not checked in this clinical study. Based on cells isolated from human RCC tumors we have identified a new mutation of the EGFR in human RCC, which could discriminate sensitive and insensitive patients to ERLO.

Conclusions: Together, our results indicate that BVZ/INF treatment could be more efficient in RCC if it is coupled to ERLO when a specific mutation of the EGFR is actionable. MET L1195F is predicted as an activating mutation (PolyPhen and SIFT) and is phosphorylated in vitro when overexpressed demonstrating the activation of MET. The MET L1195F mutant is demonstrated to be sensitive to savolitinib, a selective and potent MET inhibitor.

Disclosure: All authors have declared no conflicts of interest.
Background: Epithelial to mesenchymal transition (EMT) contributes to the metastatic and invasive potential of tumors including renal-cell carcinoma (RCC). Various preclinical and clinical results have indicated that dysregulated elements leading to EMT can be a potential target in RCC. We assessed the expression profile of EMT associated genes in surgically resected tumor tissue and targeted the survival mechanism of EMT-induced cells.

Methods: We studied the expression of epithelial marker (E-cadherin), mesenchymal markers (Snail, Slug, Vimentin, TWIST) and cancer stem cell marker (ALDH1). The median number of treatment cycles was 7. The objective response rate was 42.3% with a median duration of 11.2 months in 54 patients on EVR for breast, renal or neuroendocrine cancer. Clinical, biological and radiologic data were collected from the patients’ medical records.

Results: Epithelial marker, E-cadherin was significantly down-regulated in tumor tissue while expression of mesenchymal and cancer stem cell markers increased in tumor tissue as compared to adjoining normal tissue. EMT signature proteins showed an increase in the expression of primary cancer cells from tumor tissue as well as in EMT-induced A498 cells. We also observed increased intravasation and autophagy in EMT-induced A498 cells and primary tumor cells as compared to the normal cells. It was observed that addition of autophagy inhibitor (chloroquine) with temsirolimus to EMT-induced cells decrease their viability. Annexin-V assay showed a significant cell death in comparison of chloroquine and autophagy inhibition on EMT induction.

Conclusions: Our study shows that the process of EMT is involved in the metastatic spread of RCC and autophagy helps in survival of the EMT-induced cells. Thus, inhibition of autophagy might represent a future therapeutic option.

Legal entity responsible for the study: Postgraduate institute of Medical Education and Research, Chandigarh, India

Funding: Postgraduate institute of Medical Education and Research, Chandigarh, India

Disclosure: All authors have declared no conflicts of interest.

1551P Toward therapeutic drug monitoring of everolimus? Results of an exploratory study of the dose-exposure relationships


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Background: The efficacy of everolimus (EVR) has been demonstrated in the treatment of (i) hormone receptor-positive advanced breast cancer (ii) metastatic renal cell cancer and (iii) neuroendocrine tumours of pancreatic origin. The recommended dosage of EVR is 10 mg once daily but contrary to transplantation, therapeutic drug monitoring (TDM) of EVR is not mandatory and no blood trough levels (C0) have been defined. The aims of this study were (i) to determine C0 that could predict the occurrence of toxicities and (ii) to investigate the relationship between polymorphisms of candidate genes and C0.

Methods: This monocentric retrospective observational study was carried out over 4 months in 54 patients on EVR for breast, renal or neuroendocrine cancer. Clinical, biological and radiologic data were collected from the patients’ medical records. Toxicity was defined by temporary interruption and/or dose reduction of EVR. Patients’ exposure to EVR was dichotomized by ROC curve. The association between exposure and toxicity was then determined using a Cox model for repeated events. The impact of CYP3A4*22 and CYP3A5*3 SNPs on C0 was investigated by generalized estimating equation.

Results: Forty-two patients (77.8%) had breast cancer, 10 (18.5%) had renal cell cancer and 2 (3.7%) had neuroendocrine cancer. Toxicity (all grades) was reported in 75.9% of patients of histologically proven RCC. These were analysed in both tumor section and the adjoining normal looking parenchyma by real time PCR and Western immunoblot. In vitro studies were carried out in primary cultures and RCC cell line (A498) where EMT was induced pharmacologically using tumor growth factor beta (TGF-b, 10ng/ml). Autophagy was assessed in EVR induced cells by acridine orange staining. Tetrazolium dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay and propidium iodide (PI)-Annexin staining were done to evaluate post-treatment cell survival in EMT cells with temsirolimus and autophagy inhibitor, chloroquine.

Conclusions: Our study shows that the process of EMT is involved in the metastatic spread of RCC and autophagy helps in survival of the EMT-induced cells. Thus, inhibition of autophagy might represent a future therapeutic option.

Legal entity responsible for the study: Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, 2Department of Histopathology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, 3Department of Urology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Disclosure: All authors have declared no conflicts of interest.

1552P The role of Krüppel-like factor (KLF5) and its mechanism for treatment resistance in preoperative chemoradiation therapy for rectal cancer

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Background: The aim of this study was to determine whether Krüppel-like factor 5 (KLF5) expression in pre-irradiation tumor biopsies is a useful predictive marker of tumor response in patients with rectal cancer.

Methods: This study included 60 human colon tumor pre-irradiation specimens. Expression was studied by immunohistochemistry (IHC) using scoring system(0-15). Functional roles of KLF5 were analysed by over-expression of the protein in colon cancer cell line. Protein interactions were studied by stress induction such as chemo or radiation and MTT assays.

Results: Complete remission was achieved by 9(18%) patients. Tumor regression was significantly related with p53 and KLF5 (p = 0.021. p = 0.004 respectively). The KLF5 IHC score significantly correlated with KRAS mutation status(9.2 ± 2.4 vs 8.44 ± 1.94, p = 0.006), and ER(11 ± 2.6 vs 6.0 ± 2.43, p = 0.005). In HCT 116 cell line, KLF5 protein was significantly increased after radiation therapy, suggesting that KLF5 via cyclin D1, b-catenin. HCT 116 with KLF5 overexpression exhibited significantly better cell viability compared to control cells in MTT assay.

Disclosure: All authors have declared no conflicts of interest.

1553P The role of immune system on the efficacy of bevacizumab in patients with metastatic colorectal cancer (mCRC)

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Background: We aimed to investigate the role of anti-bevacizumab antibodies, regulatory T (Treg) and CD8+ cells on the efficacy of bevacizumab plus chemotherapy combination in patients with mCRC.

Methods: Thirty consecutive patients treated with bevacizumab plus either irinotecan or oxaplatin based chemotherapy regimens were included. The levels of Tregs (CD4 +CD25(high)FoxP3+), CD4+ and CD8+ cells from peripheral blood were assayed by flow cytometry before the onset and after 4 cycles of bevacizumab. The anti-bevacizumab antibody levels were assayed by ELISA 3 months after the onset of bevacizumab.

Results: The median age was 59 years. The majority of the patients had metastatic disease at the time of diagnosis. The chemotherapy backbone was FOLFIRI in 75% of the patients. The median number of treatment cycles was 7. The objective response (OR) and disease stabilization rates were 30% and 73.3%, respectively. The median progression-free survival (PFS) and overall survival times were 8.0 and 16.0 months. Four patients had measurable anti-bevacizumab levels. There was no OR in patients with measurable anti-bevacizumab antibody levels. The levels of Treg cells were between 0.15 and 4.82 (median 0.40) and the ratio of CD4+ /CD8+ cells between 0.91 and 4.30 (median 1.9) on peripheral blood before the treatment. There were no significant changes in the levels of Tregs and the ratio of CD4+ /CD8+ cells on bevacizumab treatment. The patients with higher CD4+ /CD8+ cells before bevacizumab had favorable PFS times (14 vs 6 mos, P = 0.065). The patients having low Treg levels after 4 cycles of bevacizumab had favorable PFS time (14 vs 7 mos, P = 0.061). The chemotherapy backbone had no significant effect on trial parameters.

Conclusions: The Treg and the ratio of CD4+ /CD8+ cells could be predictors of PFS for bevacizumab treatment in patients with mCRC. The pre-treatment ratio of CD4+ /CD8+ cells, the levels of Treg and anti-bevacizumab antibodies might influence the efficacy of long term use of bevacizumab in patients with mCRC. The improved PFS in patients having lower Treg after bevacizumab treatment may provide a rationale for the combination of bevacizumab and immune checkpoint inhibitors.

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.
Conclusions: Overexpression of KLF5 might be predictive of poor tumor regression after preoperative CRT. Our study suggests IHC of KLF5 as a possible biomarker to predict complete remission and T-down staging. Our study suggests KLF5 has a role to get resistance to chemo-therapy radiation therapy in rectal cancer treated preoperative CRT.

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Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

1555P The role of p21 activated kinase (PAK) in human colorectal cancer cell lines and resistance to cetuximab

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Background: The sensitivity to anti-EGFR targeted agents depends on the KRAS/ NRAS mutational status in colorectal cancer (CRC). Ras mutations, by disabling its intrinsic GTPase activity, increase EGFR-independent activation of PI3K/AKT and MAPK pathways. In CRC up to 25% of patients are refractory to EGFR-based therapies, even in absence of Ras mutations. We need to identify alternative signaling pathways that sustain the constitutive/activated resistant phenotype. p21 Activated Kinase (PAK) family proteins play an important role in many cellular processes, being involved in the core of cellular proliferative/transforming program. We focused our attention on the role of PAK signaling pathway in the onset of cetuximab resistance.

Methods: We used different human colorectal cancer cell lines, with distinct KRAS/ NRAS mutational status, including SW48, HCT29, HCT116, LS174T, SW403, LOVO, SW620. We also generated SW48 cells stably transfected with various KRAS mutations (G12A, G12D, G12V, G13D). We tested the effects of PAK inhibition by PF-3758389 on cell survival, cell viability and intracellular signal transduction.

Results: All the cell lines are sensitive to the PAK inhibitor PF-3758389, as shown by the inhibition of cell proliferation and cell viability, in both Ras wild type and Ras mutated cell lines. The treatment with PF-3758389 reduces the phosphorylation of various signal transducers downstream to PAK, such as MEK1 (Ser290), beta-Catenin (Ser75) and CRF (Ser388). Thus, we evaluated the downregulation of distinct PAK isoforms (PAK1, PAK2, PAK4). By western blot analysis we found a more specific inhibition of PAK2 phosphorylation after treatment with PF-3758389. Preliminary data suggest that combination of cetuximab and PF-3758389 enhances sensitivity to cetuximab in CRC cells, even in presence of Ras mutations.

Conclusions: We demonstrated that the PAK inhibitor PF-3758389 is effective in CRC cell lines, independently from the Ras mutational profile. To further study the role of different PAK isoforms, we are now performing PAK RNA silencing in both Ras wild type and Ras mutant cell lines. Based on these data, we plan to investigate the role of PAK signaling in the onset of cetuximab resistance, both in vitro and in vivo.

Legal entity responsible for the study: Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

Funding: Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

Disclosure: All authors have declared no conflicts of interest.

1556P Identification of evolutionarily conserved DNA damage response (DDR) genes that alter sensitivity to cisplatin

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Background: Cisplatin is one of the most potent chemotherapeutic agents currently in use for clinical treatment of many types of cancer, including head and neck cancers (HNCs) and epithelial ovarian cancers (EOCs). Like other platinum agents, it is thought to function primarily by modifying DNA, forming intrastrand crosslinks and other DNA lesions. The molecular mechanisms of resistance to cisplatin are not fully understood, although some forms of resistance have been associated with changes in DNA Damage Response (DDR). Identification of the new therapeutic targets would both allow a better understanding of drug resistance mechanisms, and potentially provide new avenues for disease management.

Methods: We have integrated data from a large number of functional screens performed in lower eukaryotes for genes conferring resistance to cisplatin and other DNA damaging agents such as g-ray-, X-ray-, and UV-radiation. We subsequently identified human orthologues of evolutionarily conserved genes that are potentially involved in DDR and cisplatin sensitivity in humans. We then directly tested the role of some of these genes in response to the exposure to the DNA damaging agents in EOC and HNC cell lines. We used small interfering RNAs (siRNAs) to deplete either control genes or candidate genes of interest, and under basal and drug-treatment conditions, we assessed cell viability, the impact on phospho-H2AX focus formation, and activation of the ATR DDR kinase. Besides cisplatin, we assessed gene effect on two additional DNA damaging drugs, 5-fluorouracil and olaparib.

Results: We identified in silico a set of candidate human genes with yeast orthologs that are implicated in DDR and regulation of cisplatin sensitivity in Saccharomyces cerevisiae, developing a novel genomic resource. Depletion of a set of empirically tested genes sensitized human cancer cells to cisplatin and other DNA damaging drugs, and affected phospho-H2AX foci and DDR signaling.

Conclusions: Our findings suggest that possible mechanism of sensitization to cisplatin caused by depletion of these genes involves reduced activation of DDR responses, and identifies new, non-canonical candidate regulators of DDR based on evolutionary analysis.

Legal entity responsible for the study: Kazan Federal University

Funding: This study was supported by Russian Science Foundation (project 15–15–20032).

Disclosure: All authors have declared no conflicts of interest.

1557P Next-generation sequencing of circulating tumor cells isolated from peripheral blood of patients with head and neck or gastrointestinal cancer

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Background: Real-time monitoring of tumor biology provides pivotal information for suitable therapy. Circulating tumor cells (CTCs) can reflect the current tumor status from primary sites and metastases from the bloodstream without invasive testing. The
Evaluation of exposure of regorafenib (REG) and its metabolites in pediatric patients by modeling, simulation, and clinical study

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Results: A PK model was developed based on PBPK simulations to define adult clinical study design, and to evaluate the PK data of REG and its two pharmacologically active metabolites in M-2 and M-5. A popPK model, built using data from literature and clinical studies in adult cancer patients, was used for PK simulation. Then physiological changes were integrated, including data on the growth and ontogeny of PK processes relevant for REG (e.g., cytochrome P450 3A4 activity) to scale the adult model to children. REG exposure inTCTs (6 months to 18 years) was simulated to define the PK parameters for the clinical study. A popPK model was developed based on the PBPK simulations to define the PK sampling time-points. During the study, exposure was estimated using the popPK model and compared with the PBPK simulations.

Results: Using a PBPK approach, body surface area normalized dosing was found superior compared with body weight normalized dosing. The recommended starting dose for the phase 1 study was 45 and 60 mg/m² for patients aged 6 to 24 months and 2 to 18 years, respectively. Sparse sampling with 2-5 samples per patient allowed for accurate estimation of the apparent clearance. The PBPK predictions of REG exposure were slightly higher and that of M-2 and M-5 slightly lower compared with the observed exposure in the phase 1 pediatric study. For example, in the phase 1 trial the dose of 72 and 82 mg/m², the geometric mean of the REG AUC(0-∞) based on normal dosing was estimated to be 43.1 and 50.1 mg/L/h, respectively.

Conclusion: Application of PK modeling provided an increased understanding of REG PK in pediatric patients. In addition, it allowed a sparse sampling schedule to minimize the burden for the patients in the pediatric study and supported the design of the clinical study.

Legal entity responsible for the study: Bayer

Funding: Bayer

patients/tumor characteristics and prognosis in metastatic chemo-naive tecticular germ cell tumors (TGCTs).

Methods: The study population consisted of 92 chemo-naive metastatic TGCTs patients, enrolled between July 2010 and March 2014. We analyzed 51 plasma cytokines at baseline before chemotherapy administration (n = 92) and on cycle 1 day 22 (n = 55) using multiplex bead arrays. Patients were treated with at least one cycle of cisplatin-based chemotherapy. Circulating cytokine levels were correlated with tumor characteristics, progression-free and overall survival as well.

Results: Median age was 32.4 (range 18.4-65.4) years, median follow up was 33.2 months (range 0.1-54.8). Disease progression experienced 10.9 % and 7.6 % of patients died. Several baseline cytokines positively correlated with histology, disease stage, localization of metastases, elevated baseline levels of IFN-alpha 2, IL-3R alpha, IL-16, HGF, MCP-3 significantly correlated with worse progression-free survival (PFS) and overall survival (OS) as well, SCGF-beta only with worse OS. Higher levels of IL-12p40 measured on day 22 cycle 1 correlated with shorter PFS and OS.

Conclusions: This researh study found no significant associations between circulating cytokines and prognosis and tumour/patients' characteristics in metastatic TGCTs. Our findings suggest, that plasma cytokines could be considered as biomarker for identification of high risk patients. In addition, new treatments approaches targeted for relevant cytokine should be investigated.

Legal entity responsible for the study: National Cancer Institute, Bratislava, Slovak Republic

Funding: Slovak Research and Development Agency

Disclosure: All authors have declared no conflicts of interest.

1562P Mechanisms of acquired resistance to the fibroblast growth factor receptor (FGFR) inhibitor BGJ398 in FGFR driven bladder cancer

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Background: Mutations and fusions of the FGFR3 gene occur in 10-20% of metastatic urothelial carcinoma (mUC), and recent in-vitro work demonstrates that these alterations confer sensitivity to FGFR inhibitors such as BGJ398 (Novartis). Based on these findings a phase II clinical trial of FGFR3 mutations and fusions is underway. The objective of this study was to assess potential mechanisms of acquired resistance to FGFR inhibition in order to develop rational combination therapies to enhance the efficacy of these agents.

Methods: Acquired resistance to the FGFR inhibitor BGJ398 was generated by continuous exposure of the FGFR3 fusion harboring cell lines RT4 and SW780 to increasing concentrations of BGJ398. Alterations in cell signaling components and gene expression between parental and resistant cells were assessed by western blots, phospho-kinome arrays, and qRT-PCR. Reversal of drug resistance was assessed by withdrawal of drug from resistant lines and monitoring of cell proliferation.

Results: Acquired resistance to BGJ398 in RT4 and SW780 was associated with morphological changes consistent with epithelial to mesenchymal transition. Consistent with these changes, increased mRNA expression of the mesenchymal markers Vimentin and ZEB1 and loss of expression of the epithelial marker E-Cadherin was observed in resistant cell lines. In both cell lines resistance was accompanied by an increase in pERK3/4 and a corresponding increase in expression of the ErbB3 ligand, NRG1. Additionally, resistant cell lines demonstrated an increase in pAXL levels and increased expression of fra1 mRNA, a transcriptional activator of AXL and known EMT driver. Resistant cell lines were cross resistant to alternative FGFR inhibitors such as PD173074 (Pfizer). Resistant cell lines rapidly regained sensitivity to BGJ398 after drug withdrawal of 1 month.

Conclusions: Acquired resistance to BGJ398 is associated with acquisition of an EMT phenotype, increased pERK3/4 and NRG1 expression, and increased expression of the EMT drivers Fra1 and pAXL. Preclinical study of concurrent inhibition of these pathways is underway to assess potential strategies to overcome resistance to FGFR inhibition.

Legal entity responsible for the study: N/A

Funding: Grant funding from Pfizer. BGJ398 provided by Novartis

Disclosure: A. Weckhardt: BGJ398 provided by Novartis. Research grant funding provided by Pfizer. All other authors have declared no conflicts of interest.

1563P The oncogenic role of FGFR1 depends on the molecular context

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Background: FGFR4 has been thoroughly described as an oncogene in many types of tumors, including colorectal and hepatocellular carcinoma. In lung adenocarcinoma, this receptor tyrosine kinase has been found to be one of the most mutated genes. Nonetheless, little work has been done to unravel its role in lung tumorigenesis so far.

Methods: Several lung cell lines, harbouring different genetic driver alterations with relevance in lung cancer, were transduced with plasmids to either overexpress or silence FGFR4. In these genetically engineered models several tumorigenic abilities were tested in vitro and in vivo. Besides, mRNA from formalin-fixed paraffin-embedded tissue of a cohort of lung cancer patients was extracted and FGFR4 expression levels, as well as other genes found mentioned differentially expressed genes, were measured and related to clinical characteristics.

Results: FGFR4 increases oncogenic properties in SCC cell lines, but its effects in lung ADC cell lines are context-dependent. This differential role of FGFR4 in tumorigenesis is due to differentially expressed genes between these two histologies in the cell lines under study, involving a molecular cooperation in some cases. The analysis of FGFR4 mRNA expression, together with the aforementioned differentially expressed genes, in a cohort of lung cancer patients, provided further support to our in vitro and in vivo results. High FGFR4 mRNA expression correlated with a shorter overall survival (OS) and progression free survival (PFS) in lung SCC patients. Nonetheless, longer OS and PFS were reported for the ADC patients with higher FGFR4 mRNA expression.

Conclusions: Our results show that FGFR4 oncogenic role is context-dependent and that in some cases it depends on a molecular cooperation. At a clinical level, FGFR4 mRNA expression could be a biomarker role in patient outcome. This potential prognostic role seems to be differential in the two main lung cancer histologies. The study of the molecular context of FGFR4, involving the presence of molecules with which FGFR4 is able to cooperate, could be of interest in determining the eligibility of a patient to receive FGFR-targeted therapy, or even in designing new therapeutic approaches.

Legal entity responsible for the study: CNIO-Hospital 12 Octubre

Funding: ISCIII

Disclosure: All authors have declared no conflicts of interest.

1565P Impact of a salvage chemotherapy with carboplatin plus docetaxel on testosterone levels in metastatic castration-resistant prostate cancer (mDRPC)

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Background: Recent data suggest that carboplatin plus docetaxel (DC) may be effective in mDRPC. Platinum(II)-complexes interfere with steroid biosynthesis by inhibiting
the cholesterol side chain cleavage enzyme (CYP11A1), 3β-hydroxysteroid dehydrogenase (HSD3B1.2) and 17α hydroxylase/C17,20-lyase (CYP17A1).

Methods: Docetaxel failure/resistance was defined according to the Prostate Cancer Working Group (PCWG2 2007) criteria. Treatment consisted of at least two cycles of carboplatin AUC5 in 30 min on day 1 every 4 weeks, docetaxel at a dose of 35 mg/m2 iv for 1 hour on days 1, 8, 15 plus prednisone 25mg/day orally after receiving informed consent until disease progression or occurrence of intolerable adverse effects. Efficacy measures were done following PCWG2 recommendations. In the post-treatment/androgen levels were measured before (n = 73) and during docetaxel/docetaxel chemotherapy (n = 63).

Results: Of the 96 pts. treated since February 2005, 95.8% had bone, 42.7% lymph node, 26.0% liver and 19.8% lung involvement. At the current analysis, the median follow-up time was 14.6 months. 86 pts. had died and 90 had progressive disease. The objective response rate was 22/59 (37.3%). Response of prostate specific antigen (≥50%) was observed in 48/96 (50%) patients. Median based on patients progress target group was 7.2 months (CI 95% 6.3, 8.1) and median OS was 15.6 months (CI 95% 11.6, 19.7). The most common reversible grade 3/4 toxicity was leucopenia/neutropenia (39.6/ 33.3%). Median free testosterone levels were 6.63 ng/ml before and <0.18 pg/ml during carboplatin/docetaxel (p < 0.03) and median 17α-hydroxysteroid levels were 2.58 ng/ml before and <0.18 pg/ml during carboplatin/docetaxel (p < 0.03). Median serum androgen levels (T + DHT) were 0.1 ng/ml before and below the detection limit of <0.05 ng/ml during DC treatment. In multivariate analyses, LDLH, PSA response, free testosterone nadir levels below the detection limit (<0.18 pg/ml) during DC treatment were associated with longer OS (p < 0.05).

Conclusions: These data suggest that carboplatin plus weekly docetaxel may be an important second-line treatment option for DPSC pts. by inhibiting the testosterone biosynthesis.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

1567P Adenovirus-based antibody screening method and EphA2-targeted therapy

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Background: Development of a system that allows selective drug delivery into a cancer cell is expected to enable targeted therapy. We constructed a genetically modified adenovirus vector incorporating an IgG Fc-binding motif from staphylococcal protein A, Z33 (Adv-FZ33). Adv-FZ33 allows an antibody to redirect the vector to a target molecule on the cell surface. We attempted to search for target antigen candidates and antibodies that allowed highly selective gene transduction into malignant tumors.

Methods: Hybridoma libraries producing monoclonal antibodies (mAb) were screened that increased transduction efficiency in cancer cell lines after cross-linking with Adv-FZ33. Target antigens of the mAbs were identified by immunoprecipitation and mass spectrometry. Of these mAbs, we noted a clone, F2-27, that recognized the receptor tyrosine kinase EphA2. Next, we generated an adenovirus vector, Ax3CMTK-FZ33 that expressed a herpes simplex virus thymidine kinase (HSV-TK). The therapeutic efficacy of F2-27-mediated HSV-TK gene transduction, followed by ganciclovir (GCV) administration, was studied in vitro. The inhibitory effect of F2-27 on cancer cell invasion was investigated by a three-dimensional spheroid formation assay.

Results: In vitro reporter gene expression after Adv-FZ33 infection via F2-27 was 146 and 236 times higher than with control mAb or vector alone in EphA2-expressing cancer cell lines. F2-27 mediated antitumor effect of HSV-TK/F2-27 infection induced the HSV-TK gene in a F2-27-dependent manner, and had a highly effective cytotoxic effect, in a GCV-dependent manner, on EphA2-positive cancer cell lines; the IC50 of GCV in F2-27 treated, and that in isotype control mAb-treated cells was 0.37 ng/ml and 39.28 ng/ml under the condition of a 1,000 VP/cell infection, showing a significant 106-fold difference. Additionally, F2-27 independently inhibited migration of EphA2-positive breast cancer cell lines in three-dimensional culture.

Conclusions: Our modified adenovirus and hybridoma screening system is useful for the development of targeted cancer therapy, and F2-27 has the potential to be an antibody-based therapy for various EphA2-positive cancers.

Legal entity responsible for the study: Fukuoka University

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tested. These magnets will also be used in the mice studies with laser-driven protons and for experimental gantry design studies at conventional therapy beamlines.

Conclusions: Substantial progress has been made towards clinical application of promising laser-driven proton therapy although further development is required.

Legal entity responsible for the study: Technical University Dresden

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Disclosure: All authors have declared no conflicts of interest.

1569P Time structure influence on the radiobiological response to MeV electron beams

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Background: In current clinical radiotherapy electron, photon and ion beams are delivered (quasi-) continuously with typical dose-rates of a few Gy/min. Recent developments in dose delivery like IMRT and respiratory-gated treatment as well as accelerator techniques like flattening filter free Linacs and laser-based particle accelerators are driven towards intermittent irradiation with higher dose rates. Compared to continuous dose delivery these new techniques differ not only in dose rate, but also in the temporal sequence of pulse delivery, i.e., pulse lengths and pulse intervals. Previous studies on the influence of high dose rates were focussed on single pulse electron exposure and vary in energy, pulse duration and cell line; the impact of intermittent irradiation was rarely investigated. In the present work, the influence of dose rates of up to 10^12 Gy/min and of intermittent irradiation with pulse lengths and pulse intervals in the range of seconds were studied.

Methods: The radiation source ELBE (Electron Linac for beams with high Brilliance and low Emission) was used to mimic intermittent irradiation with asymmetric split-doses, separated by pulse intervals in the range of 10 ms to 90 s, and the quasi-continuous electron beam of a clinical LINAC. Using the HINSCC line SQ02B the impact of pulse structure was analyzed by clonogenic survival assay. Moreover, the LINAC-like electron beam and electron pulses with pulse dose rates of up to 10^12 Gy/min were used to measure the kinetics of g-H2AX/53BP1 foci disappearance up to 24 h after treatment as a surrogate marker for DNA double-strand break complexity in the process of qualification of the biomarker and its performances need to be more investigated. The ADC bias error was about 6%, meaning the ADC measured is close to the theoretical value of 1.1*10^-3 mm²/s for the 0°C water. ADC b-value dependence and ADC spatial dependence were respectively 0.5% and 3% and passed the test. With this as an effect on how long patients stay on cytotoxic or targeted treatments.

Results: In general, the radiation response was found to be independent from electron pulse structure for the two endpoints under investigation.

Conclusions: These results reveal that ultra-high pulse dose rates of 10^12 Gy/min and of intermittent irradiation with pulse lengths and pulse intervals in the range of seconds were studied.

Legal entity responsible for the study: Helmholtz-Zentrum Dresden-Rossendorf

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Disclosure: All authors have declared no conflicts of interest.

1570P ‘Research’ vs ‘real world’ patients: the representativeness of clinical trial participants

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Background: Randomized Clinical Trials (RCTs) are the gold standard in assessing the efficacy of new treatments as they allow for the analysis of a homogenous study population. However restricting the eligibility criteria may result in cherry-picking RCT participant thus compromising the generalisability. We have investigated differences in certain prognostic factors between trial and non-trial patients to see if this has an effect on how long patients stay on cytotoxic or targeted treatments.

Methods: IMS Health Oncology Analyzer™, a patient database collected through a quarterly physician panel survey was used. Data includes Stage IV, NSCLC, Colorectal (CRC) and Pancreatic Cancer (PC) patients within EU5 (France, Germany, Italy, Spain, UK) reported between 2013 and 2015. For the initial analysis the prognostic factors compared are ECOG, Co-morbidities and Age. For the secondary analysis the obtained results do not perfectly fit with the QIBA expectations. The diffusion weighted MRI images were obtained using a multishot SS-EPI sequence with b-values 0, 100, 600 and 800 s/mm². Mean ADC and standard deviation ADC were measured over a spherical volume of interest (diameter: 4cm) placed at the center of the 0°C water cylinder (Diameter: 5 cm). To assess the spatial dependence, another acquisition was performed with the phantom in a different orientation. ADC bias error, ADC random error, ADC b-value dependence, ADC signal to noise ratio and ADC spatial dependence were assessed.

Results: The results revealed that ultra-high pulse dose rates of 10^12 Gy/min and of intermittent irradiation with pulse lengths and pulse intervals in the range of seconds were studied.

Conclusions: Our data supports the existence of prognostic differences between ‘Trial’ and ‘Real World’ patients. Even though we have not observed an effect of this on DOT, further analysis is required to study the array of clinical and survival outcomes that prognostic differences are likely to impact. The next step is a comparison of parameters such as response to therapy, adverse events and Progression Free Survival to further analyse the representativeness of RCTs.

Legal entity responsible for the study: IMS Health

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Disclosure: All authors have declared no conflicts of interest.

1571P Reliability of apparent diffusion coefficient assessments according to the QIBA guideline

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Background: Apparent Diffusion Coefficient (ADC) is an emerging quantitative imaging biomarker in oncology obtained from MR imaging. This index might predict tumor aggressiveness and therapy response at baseline. The Quantitative Imaging Biomarkers Alliance (QIBA) published a guideline to assess the reliability of ADC. Our study aims at testing the implementation of QIBA guidelines and confirm the expected results. This is a first step before assessing response thresholds of ADC for patient monitoring.

Methods: An ice-water phantom was scanned on an Optima MR 450W 1.5T (GE) following the QIBA quality control protocol. The diffusion weighted MRI images were obtained using a multishot SS-EPI sequence with b-values 0, 100, 600 and 800 s/mm². The obtained results do not perfectly fit with the QIBA expectations. The diffusion weighted MRI images were obtained using a multishot SS-EPI sequence with b-values 0, 100, 600 and 800 s/mm². Mean ADC and standard deviation ADC were measured.

Results: The obtained results do not perfectly fit with the QIBA expectations. Therefore, these data deserve further analysis and the QIBA guidelines likely to be discussed. Even if the clinical value of ADC has been put in evidence by several groups, the process of qualification of the biomarker and its performances need to be more documented.

Legal entity responsible for the study: N/A

Funding: Centre Antoine Lacassagne, Nice, FRANCE

Disclosure: All authors have declared no conflicts of interest.

1572P Current and future next generation sequencing usage in European molecular oncology diagnostics

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Background: The integration of next generation sequencing (NGS) into clinical molecular diagnostic (MoDx) laboratories has been growing and continues to expand into new applications for molecular oncology, but is hampered by technical challenges. In order to better meet the needs of diagnostic testing, it is necessary to understand the current and planned adoption of NGS systems as kits, both commercial and laboratory developed, must be optimized for specific machines.

Conclusions: Our data supports the existence of prognostic differences between ‘Trial’ and ‘Real World’ patients. Even though we have not observed an effect of this on DOT, further analysis is required to study the array of clinical and survival outcomes that prognostic differences are likely to impact. The next step is a comparison of parameters such as response to therapy, adverse events and Progression Free Survival to further analyse the representativeness of RCTs.

Legal entity responsible for the study: N/A

Funding: Centre Antoine Lacassagne, Nice, FRANCE

Disclosure: All authors have declared no conflicts of interest.
Methods: We surveyed >3000 labs throughout Western Europe and will here focus on NGS usage in general and overall molecular methods for BRCA, Braf, Ras, and EGF in Germany (DE), Italy (IT), and the UK. Telephone interviews were conducted in 2015 and 2016 with data collected on technologies, systems and kits used, test volumes, and planned NGS systems and markers in the next 5 years.

Results: Usage of NGS systems is increasing, though this varies by country, with DE being slowest to adopt where only 7% of MoDiXs labs have an NGS and 30% of systems used for oncology MoDiXs are still Sanger sequencers. Most molecular oncology done in IT is on RT-PCR (51%) systems, followed by NGS (34%). The UK has the highest NGS usage for oncology (52% of systems). Overall, ~17% of MoDiXs labs in Europe have an NGS machine and, of those not currently running NGS, another 23% plan to acquire it in the next 5 years. Sixty-five percent of those reporting a preference chose Illumina systems. There is a growing focus on benchtop sequencers seen in the dominant presence of Illumina’s MiSeq® (35%) and Theramo Fisher Ion sequencers (29%) out of all current NGS systems and future planned systems (90% reporting intent to acquire Illumina systems stated this would be a MiSeq®).

Conclusions: Current top molecular oncology testing includes EGFR, BRAF, Ras, and BRCA and these will remain widely tested in the near future along with increasing use of NGS systems. Further, three SNPs on each of these NGS systems will help grow clinical NGS usage as they’re cheaper and faster but there is still a need for increased automation, more panels, and easier result reporting. As NGS usage in labs becomes standardized and more requested by oncologists, this will push payers to improve reimbursement strategies allowing for improved clinical patient care.

Legal entity responsible for the study: di Healthcare GmbH: a consulting and market research firm operating solely in the area of in-vitro diagnostics

Funding: di Healthcare GmbH: a consulting and market research firm operating solely in the area of in-vitro diagnostics

Disclosure: All authors have declared no conflicts of interest.

1573P A candidate gene study for oxaliplatin induced chronic peripheral neuropathy (OICPN) based on a priori genome wide association study (GWAS)

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Background: Peripheral neuropathy complicates oxaliplatin therapy and occurs in two forms; a transient cold-induced neuropathy and a chronic form which requires dose reduction, early cessation, or causes long term morbidity in a proportion of patients. Various studies have suggested a complex pharmacogenetic susceptibility may exist to account for inter-individual variation in occurrence and severity of OICPN, but results are frequently contradictory or unvalidated. We performed a systematic review of the literature which identified two East Asian studies suggesting a role for three SNPs; a transient cold-induced neuropathy and a chronic form which requires dose adjustment or cessation of oxaliplatin. Controls experienced a maximum of 1.65 ± 0.23; RV: 1.71 ± 0.13 and 1.98 ± 0.90 LFC, resp.) or BCL3 (LV: 2.97 ± 0.34 and 2.96 ± 0.79; RV: 4.81 ± 1.01 LFC, resp.).

Conclusions: Miyers® proved to be less cardio toxic as compared with DOX, resulting in better cardiac function and less fibrosis. However, both cytotoxic treatments led to overexpression of collagen-associated genes and proto-oncogenes, which might explain the development of myoccardial fibrosis and secondary malignancies.

Legal entity responsible for the study: Mariann Gyongyosi

Funding: TEVA ratiopharm provided the Department of Cardiology, Medical University of Vienna, with NPL-doxorubicin and an unrestricted grant, but was not involved in the study protocol, data acquisition, data analysis or the writing of the abstract.

Disclosure: M. Gyongyosi: Funding: TEVA ratiopharm provided the Department of Cardiology, Medical University of Vienna, with NPL-doxorubicin and an unrestricted grant, but was not involved in the study protocol, data acquisition, data analysis or the writing of the abstract. All other authors have declared no conflicts of interest.

1575P 5-Fluorouracil (5FU) intratumoral pharmacokinetics: Rapid uptake in cells and in spheroids (SPH)

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Background: Limited data are available on 5FU intratumoral pharmacokinetics. Previous studies with radiolabeled 5FU showed homogeneous uptake in spheroids within a few minutes (Cancer Chemother Pharmacol. 1984;13(2):131-5) but no quantification was done. We present data on intracellular and intra-spheroidal 5FU uptake; drug efflux experiments are on-going and results will be presented.

Methods: MCF-7 and HCT-116 cells were used for cellular and spheroid experiments. Spheroid growth was optimized to produce a spheroid of 300-400 μm diameter at day 4. Treatment: 1x106 cells or 30 spheroids/tube time point were exposed to 10 μM (1300ng/ mL) SFU at <1, 5, 10, 20, 40, 60, 120 and 240min, then washed x3 with PBS. Acetonitrile was added to the pellet, sonicated and the supernatant evaporated and reconstituted with mobile phase. Simultaneous quantification of 5FU, 5-Fluorouridine (5FUdR), 5-fluoro-2-deoxyuridine (5FdUrD) and 5-fluorouracil (internal standard) was achieved by HPLC-Tandem Mass Spectrometry. Each experiment was carried out in triplicate; pharmacokinetic curves were derived using GraphPad Prism 6. We will also measure 5-fluoro-2-deoxyuridine-5'-monophosphate (5FDUMP).

Results: Both MCF-7 and HCT-116 achieved steady state by 20min in cells (1800g/appr.) and 40min in spheroids (330ng/g/appr.) that was maintained at 240min. No 5FdUrD was seen but SFUdR was identified in the HCT-116 cell line, with SFUdR included, total drug levels at steady state were 3080ng/g and 1000ng/g in cells and spheroids, respectively. Although there was variability in the HCT-116 drug levels between experiments, the contour of the drug uptake curve was consistent. MCF-7 spheroids are being analyzed.
Conclusions: Our results suggest that SFU is rapidly taken up into cells and spheroids, being less prominent in spheroids. These data and methodology may be useful to allow generation of mathematical models to improve drug delivery.

Legal entity responsible for the study: Institute Cancer Therapeutics (Bradford University) / University of Leeds

Funding: Institute Cancer Therapeutics Spanish Medical Oncology Society

Disclosure: All authors have declared no conflicts of interest.
Results: In transduced cells, TRAIL mRNA levels were 40,000 fold higher with a concurrent 5 fold higher protein expression. TRAIL mRNA and protein levels increased when the cells were co-cultured with U266 cells, or in presence of IL-1α and IL-1β, whereas the MM cell apoptosis after 48 hrs was 70.3 ± 3.5% compared to 20.5 ± 2.3% of control UC-MSCs. Significant reduction of MM tumor masses were detected in mice injected with TRAIL+-UC-MSCs, as compared to control mice (p < 0.05).

Conclusions: Our data support the TRAIL+-UC-MSCs approach to treat MM in NOD-SCID mice. Besides their migratory property to the MM microenvironment, TRAIL+-UC-MSCs reinforce their constitutive anti-MM activity by TRAIL over-expression.

Legal entity responsible for the study: Prof. Franco Silvestris
Funding: AIRC (Associazione Italiana per la Ricerca sul Cancro)
Disclosure: All authors have declared no conflicts of interest.

A multicellular 3D cell culture model for investigation of endothelial cell migration
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Background: We are experiencing a transition from disease to target-oriented therapy due to the increasing understanding of the mechanisms relevant to the genesis of cancer. One major hurdle for the development of these targeted therapeutic regimens, however, is the limited availability of predictive in vitro models. We present data that highlights the differences of RNA expression of in vivo like 3D microtissues consisting of tumour cells, fibroblasts and two different endothelial cell lines compared to normal 2D cell culture conditions.

Methods: 96-well hanging drop microtiter plates (InSphero AG, Zürich, Switzerland) were applied for the production of 3D mono-, co- and tri-cultures including the human lung cancer cell lines A549 or Colo699 alone or in combination with a human lung fibroblast cell line (SV-80) and either a human umbilical vein endothelial cell line (HUVEC) or the primary human lung microvascular endothelial cell line (HMVEC-L). Tumour endothelial spheroid aggregation was displayed immunohistochemically (IHC) by protein expression of e-cadherin, CD31, von Willebrand factor (vWF) and α-muscle actin (α-SMA). RNA expression profiling by Affymetrix chip analysis was performed for multicellular 3D microtissues and 2D cultured cell lines. Bevacizumab was added in different doses and inhibition of endothelial cell migration and drug related toxicity was displayed either by flow cytometry or IHC.

Results: In microtissues, endothelial cells aggregated in coherent tube-like structures preferentially in the fibroblast consisting core of all microtissues. However, inhibition of vascular endothelial growth (VEGF) factor by bevacizumab led to an in part blockade of endothelial cell migration into the microtissues. Nevertheless, no toxic effect of this drug was displayed either on tumour cells, fibroblasts or endothelial cells. RNA expression profiles revealed a high number of regulated genes in tri-cultures when compared to microtissues only consisting of mono- or co-cultures or to traditional 2D cultured cells.

Conclusions: In this work, we demonstrate a functional multicellular model consisting of tumour cells, fibroblasts and endothelial cells that allows the investigation of anti-angiogenic drugs.

Legal entity responsible for the study: Medical University Innsbruck Tirol Kliniken
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tumour biology and pathology

Copenhagen prospective personalized oncology (CoPPO): Genomic profiling to select patients for phase 1 trials

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Background: Advanced technologies can be used to portray genomic alterations (GA) that potentially drive tumor growth. We have established a sequencing and array based pipeline to identify GA to select patients (pts) who might benefit from novel targeted treatments and to enrich the population in phase 1 trials with pts that harbor specific targets. A total of 380 pts are referred annually based on 25 ongoing phase 1 trials.

Methods: Adults with advanced solid tumors referred to a dedicated Phase 1 Unit were offered biopsy for mapping of GA. Three fresh tumor 18 G needle biopsies were taken, two were stored in RNAlater® (Life Technologies) for RNA expression analyses and DNA gene mutation analyses, while one biopsy was formalin-fixed and paraffin-embedded for histopathological analyses to confirm suitability of the material, including the presence of min. 100 tumor cells. SNP-array from tumor and whole exome sequencing (WES) from DNA (tumor and blood) were performed using sequence capture and Illumina sequencing to call tumor somatic mutations. WES from blood was used to subtract germline polymorphisms. Expression levels of therapeutic targets were revealed by expression Array and RNA-seq from tumor RNA. A tumor board reviewed results. Pts with specific GA that could be targeted with drugs in development were enrolled in phase 1 trials. Individualized treatment with marketed drugs (Off-label) or non-approved drugs (Named pt program) were offered according to level of existing evidence.

Results: Between May 2013 and April 2016, we screened 366 heavily pretreated pts with solid tumors. In 297 pts (81%) a biopsy was taken. In 283 (77%) we achieved sufficient tumor tissue to perform a full genomic profile. An actionable target was found in 235 pts (75%) out of 383 pts. Mean time from biopsy to reporting of results was 36 days. 133 pts with an actionable target were eligible for treatment. 57 pts (20%) were treated according to the findings of either mutations or RNA expression levels of treatment targets in phase 1 trials (N = 39) or Off-label treatment/Named pt (20%) were treated according to the findings of either mutations or RNA expression levels. In 297 pts (81%) a biopsy was taken. In 283 (77%) we achieved sufficient tumor tissue to perform a full genomic profile. An actionable target was found in 235 pts (75%) out of 383 pts. Mean time from biopsy to reporting of results was 36 days. 133 pts with an actionable target were eligible for treatment. 57 pts (20%) were treated according to the findings of either mutations or RNA expression levels of treatment targets in phase 1 trials (N = 39) or Off-label treatment/Named pt program (N = 18).

Conclusions: Establishing and array-based pipeline for enrichment of patients to phase 1 trials is feasible in a Phase 1 Unit.

Clinical trial identification: NCT02290022

Legal entity responsible for the study: Righospitalet, Copenhagen

Funding: Region H

Disclosure: All authors have declared no conflicts of interest.

Analysis of circulating cell-free DNA in plasma shows a higher detection rate of EGFR mutations in patients with extrapulmonary disease progression

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Background: Noninvasive monitoring of EGFR mutations conferring sensitivity (i.e., L858R and various types of exon 19 deletion mutations) and resistance (i.e., T790M and C797S) to tyrosine kinase inhibitors (TKIs) is vital for efficient genotyping of adenocarcinoma (LADC) with conventional and/or new generation EGFR-TKis. Although plasma cell-free DNA (cfDNA) is detectable at an early stage, the size of the tumors does not significantly correlate with cfDNA concentration. We explored clinical features of patients with LADC whose cfDNA examination was useful.

Methods: Forty-four plasma samples from 37 LADC patients receiving EGFR-TKI therapy, including 20 who developed resistance, were prospectively subjected to droplet digital PCR (ddPCR) analysis to determine the fraction of cfDNA with EGFR mutations, and analyzed according to clinical features. The factors subjected to analysis were age, sex, ECOG PS, sites of metastatic disease, and sites of recent progressive disease.

Results: cfDNA samples from 19 (95%) of the 20 resistant patients were positive for TKI-sensitive mutations as previously reported. Also, 26 (84%) of 31 patients with extrapulmonary disease progression, and 24 (86%) of 28 with regional lymph node metastases, were similarly positive: cfDNA analysis from patients with these features correlated with a high detection rate of TKI-sensitive mutations (adjusted risk: detection rate: 2.726, 95% CI: 1.189-6.250; lymph node metastases: risk ratio: 2.095, 95% CI: 1.952-4.174). Presence and sites of metastatic diseases were not correlated with detection rate significantly.

Conclusions: EGFR mutation detection from cfDNA is useful in EGFR-TKI resistant patients, especially those with extrapulmonary disease progression. One possible explanation for this difference is that migration potency of tumor cells might increase the amount of plasma cfDNA by promoting the dissemination of tumor cells into plasma. Further analysis of cfDNA from patients with these features may be useful for tumor molecular profiling and treatment modification.

Clinical trial identification: The study was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN 000017581).

Legal entity responsible for the study: Yutaka Fujiwara

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Unsupervised latent class analysis of adult glioma variant profiles reveals biologically and clinically relevant subclasses

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Background: Adult gliomas represent a diverse group of tumors characterized by differing genetic signatures and clinical presentations. Using unsupervised latent class analysis (LCA) of glioma somatic variants (independent of diagnosis), we identified biologically and clinically relevant subclasses associated with distinct clinical outcomes while highlighting the landscape of glioma driver events.

Methods: LCA was performed on somatic variants from 765 adult glioma patients (grade II-IV, TCGA dataset) using expectation-maximization and Newton-Raphson algorithms to determine maximum likelihood estimates of model parameters. Survival outcomes per class were generated using Kaplan–Meier and COX proportional hazard analysis.

Results: LCA revealed seven distinct classes of gliomas. Classes 1 and 2 were defined by IDH1/2 mutations. Class 1 showed co-occurring CIC mutations and 1p/19q co-deletion (oligodendroglial lineage) whereas Class 2 enriched for co-occurring TP53 and ATRX mutations (astrocytic lineage). Class 3 was characterized by dysregulated cell cycle signaling largely due to alterations in MDM2/CDK4 whereas Class 4 enriched for activation of PI3K signaling mediated through alterations in NF1, PIK3CA, and PTEN. Receptor tyrosine kinase activation including EGFR and PDGFRα/KDR/Kit defined Class 5 and 7, respectively. Class 6 enriched for gliomas with gains of chr 7 but without IDH1/2 (2907 days Class 1, 2000 days Class 2) and poorest for Class 4 (383 days).

Conclusions: LCA of glioma somatic variants reveal biologically and clinically relevant classes independent of diagnosis that are associated with significant differences in patient survival. The genomic classes seem to involve different underlying molecular mechanisms that can become altered in gliomas. These findings suggest that LCA-based glioma classification may serve as a primary predictor for clinical outcomes and provide objective data to be used in clinical management and trial design.

Legal entity responsible for the study: Foundation Medicine

Funding: Foundation Medicine

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Background: Previous studies suggest that breast cancer dissemination is not only driven by the tumor somatic alterations but also by the host's genetic background. The main objective of this study is to identify germline genetic variations predictive of metastatic dissemination in breast cancer patients.

Methods: Breast cancer patients with discordant extreme phenotypes were selected for a genome-wide association study (GWAS). Low risk patients (<2cm and no lymph node involvement) that unexpectedly relapsed within 5 years after surgery and high risk patients (>10 positive lymph nodes) without relapse. Patients were distributed in a discovery set including controls (low risk without relapse and high risk with relapse) and a validation set. Around 4.3 million SNPs were genotyped with the Illumina platform.

Results: One of the top SNPs was rs28452734 (p = 3.43x10^-5, OR = 9.86 in validation set). This SNP is located near XYTL1, a gene involved in the biosynthesis of glycosaminoglycan chains which form the extracellular matrix. XYTL1 has been previously associated with adhesion, proliferation, angiogenesis and metastasis. In turn, the pathways analysis identified an enrichment of genes from KEGG pathways including ECM-receptor interaction and cell adhesion and in three pathways previously published in association with metastasis 1) PIK3CA multipotent genetic program 2) early-stage metastatic disease or low burden signature 3) essential integrins and organ-specific metastasis.

Conclusions: These results suggest that there may be an association between patient’s germline genetic background and breast cancer prognosis, independently or in conjunction with intrinsic tumor alterations.

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Germline genetic background contribution to metastatic dissemination in breast cancer extreme phenotype patients

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Different breast tumor morphological structures reflect specific EMT states and contribute to cancer metastasis

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Background: Epithelial-mesenchymal transition (EMT) is an obligatory event during invasion and metastasis and contributes to tumor progression. Intraductal morphological heterogeneity of invasive carcinoma no special type (IC NST), represented by five types of morphological structures: tubular, trabecular, solid, alveolar structures, and discrete groups of tumor cells, is associated with tumor progression. The presence of alveolar structures in the tumors of untreated patients is linked with lymph node metastasis (Zaryalova et al., 2013), however the mechanism of this fact is unknown. The aim of this work was to estimate the association between morphological structures and metastasis frequency in the chemotherapy treated patients and to study gene expression profile of the structures.

Methods: 438 IC NST patients (mean age 50.5 (±0.58 SD), TNM) treated with neoadjuvant chemotherapy have been enrolled. SurePrint G3 V2 8x60K gene expression arrays were used to analyze transcriptome of morphological structures, isolated from fresh tumors (n = 3) by laser microdissection.

Results: Patients with alveolar or trabecular structures or discrete group of cells in breast tumors more frequently displayed lymph node metastasis than cases without these morphological variants (65.3% vs. 33.2%, p = 0.0001; 58.7% vs. 36.3%, p = 0.0001; 59.4% vs. 41.3%, p = 0.0002, respectively). The presence of alveolar or trabecular structures was associated with high frequency of distant metastasis in comparison with cases without these structures (42.8% vs. 27.3%, p = 0.0036, 41.9% vs. 20.7%, p = 0.005, respectively). Cluster analysis of morphological structures showed the following phylogeny: alveolar and trabecular - solid - trabecular - discrete groups of tumor cells. Furthermore, different structures showed specific set of epithelial (EpCAM, CD44, CD34, CD57) and mesenchymal (Vim, MMP2, CD11, CD142) markers with prevalence of E in alveolar and M in discrete groups of tumor cells.

Conclusions: Five types of morphological structures of IC NST may represent different EMT states and thus contribute to tumor metastasis. Research is supported by Russian Science Foundation Grant: No. 14-15-00318

Legal entity responsible for the study: Tomsk Cancer Research Institute

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Tumor infiltrating lymphocytes and tertiary lymphoid structures in paired primary tumors and metastases from breast cancer patients

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Background: In primary tumors (P), infiltrating lymphocytes (TL) and tertiary lymphoid structures (TLS) have been associated with better clinical outcomes, in HER2
Methods: We analyzed formalin fixed paraffin embedded tissue samples from a retrospective cohort of BC patients who underwent adjuvant surgery for the P and metastasis. The tissue was stained by anti-CD3 (T cells) and anti-CD20 (B cells) antibodies in a double stain were scored by two trained pathologists blinded to the clinical data. TIL were scored as the percent (%) of stroma plus tumor area infiltrated with CD3+ plus CD20+ cells. The number of TILs were normalized to the tumor area.

Results: The extent of TIL in P (range 1-35%) was significantly higher with respect to the corresponding M (p = 0.04). Interestingly, when the extent of TIL in P was ≥10% (<TIL>) there was a significant decrease in the TIL detected in M (p < 0.0001, n = 20). Alternatively, when TIL infiltration in the P was <10% (TIL<) the TIL was significantly higher at the distant M site (p = 0.002, n = 21). In secondary M lesions, TIL increased from 20% to 25% in TIL< and were essentially absent. Analysis of TIL in M from different organs revealed a significantly higher level in soft tissues (n = 4) compared to skin (n = 24), brain (n = 2) or breast relapses (n = 14) (p = 0.04).

Conclusions: These preliminary data suggest that tumors can alter their immunogenicity during disease progression by their production of neutrogens and/or immunosuppressive factors, which potentially accounts for our observed differences between P and M. In metastatic disease, the extent of immune infiltration is globally lower than in early disease with almost no TIL found in M, signifying that the composition and organization of the immune infiltrate varies between disease stages. The extent of the immune infiltrate may also depend upon the organ site of relapse, further complicating the heterogeneity of both the tumor and the anti-tumor immune response.

Legal entity responsible for the study: Université Libre de Bruxelles

Funding: Les Amis de l’Institut Jules Bordet

Disclosure: All authors have declared no conflicts of interest.
Background: Mucinous ovarian tumors (MOT) are among the rarest and least studied epithelial ovarian neoplasms. Teratoma-associated MOT have been shown to be of germ cell origin. However, the pathogenesis of MOT not associated with teratoma remains unclear. Recent exome sequencing studies revealed similarities between MOT and mucinous cystic neoplasms (MCN) of the pancreas with frequent mutations in KRAS and RNF43.

Methods: Here we investigated the clinical characteristics of a series of 23 MCN and 287 MOT, which included age at diagnosis, sex, stage and exposure to smoking. We compared the immunohistochemical patterns of 23 MCN and 18 MOT (CK7, CK20, CDX2, MUC2, MUC5AC, SMAD4 and β-catenin). We analyzed the germline profile (GEP) of 19 normal pancreatic tissues, 36 pancreatic ductal adenocarcinomas (PDAC), 6 MCN, 8 MOT, 27 normal fallopian tube (FT), 13 high-grade serous ovarian carcinomas (HGOSC), 6 ovarian surface epithelium (OSE), 2 human PGCs and single cell RNA-sequencing of 5 primordial germ cells (PGC).

Results: We observed that both MOT and MCN occur mainly in young women that have been exposed to smoking and they are frequently diagnosed at early stages. Both tumors have similar immunohistochemical phenotype, mainly CK7 + CK20-MUC2-CDX2+. Thus, we hypothesize that MCN and MOT would share a common cell of origin, primordial germ cells (PGCs) that stopped in the dorsal pancreas during their descent to gonads during early human embryogenesis. We compared GEP of MOT, HGOSC, OSE, FT and PGCs. Alterations in MOT correlated more with PGCs whereas HGOSC correlated with OSE or FT. We also compared GEP of MOT, HGSOC, OSE, FT and PGCs. Molecular alterations in pancreatic MCN correlates better with PGCs whereas PDAC relied on normal pancreatic tissue.

Conclusions: These findings support a common molecular pathway for the development of MCN and MOT and suggest that both tumors can derive from PGCs. These findings could explain the similar clinical presentation and the frequent presence of the β-catenin gene alteration in both tumors.
using logistic model. Cox and Snell's R^2, Nagelkerke's R^2, Bayesian information criterion (BIC) and ROC curves (AUC) values were used for assessing the fitting ability of obtained models.

**Results:** Two strategies for multiclass classification were used. One-vs.-one (OvO) compares grade pairwise and then builds a binary classifier for each grade. One-vs-all (OvA) strategy involves training classifier based on comparing the grade to the set of others. Logistic regression model was selected as binary classifier. As a result large varieties of models were built including different set of predictors. Models with the best accuracy were selected for each strategy (Table). G2 vs. G3 includes such predictors as tumor expression rate of Bcl-2 and p53. And these predictors are included in G3 vs. All. Pointing that the main effect induced by G2 and G3. But G2 vs. G3 has better accuracy (AUC = 0.8). G1 vs. G2 includes number of NOBs total volume of NOBs and average DNA content in the cells. G1 vs. All includes the same predictors too but shows better accuracy (AUC = 0.74).

## Table: 1594P

<table>
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<th>χ^2</th>
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<td>G1 vs. G2</td>
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<td>G2 vs. G3</td>
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<td>0.39</td>
<td>0.54</td>
<td>0.89</td>
<td>0.80</td>
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<tr>
<td>G3 vs. G1</td>
<td>19.52</td>
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<td>0.0002</td>
<td>0.39</td>
<td>0.54</td>
<td>0.89</td>
<td>0.80</td>
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<tr>
<td><strong>OvA</strong></td>
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<tr>
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<td>0.16</td>
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<td>G2 vs. All</td>
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<tr>
<td>G3 vs. All</td>
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<td>0.008</td>
<td>0.12</td>
<td>0.23</td>
<td>0.13</td>
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</table>

**Conclusions:** Therefore, models from different strategies can be combined into a novel one. In our case G1 vs. All and G2 vs. G3 may be used together for colorectal tumor grading in an hierarchical manner. First off G1 separates from group of G2 and G3 with the following G2 and G3 separation.

**Legal entity responsible for the study:** National Cancer Institute, Department of Pathologic Anatomy; 33/43, Lomonosova str., Kyiv, 03022, Ukraine

**Funding:** Ministry of Healthcare of Ukraine

**Disclosure:** All authors have declared no conflicts of interest.

## 1595P MicroRNAs as biomarkers of resistance to HER2 inhibitors in combination with chemotherapy in gastro-oesophageal cancer cell lines

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**Background:** MicroRNAs (miRs) may be involved in primary resistance to HER2 inhibitors and represent a clinically useful biomarker for gastro-oesophageal cancer (GOC) patients with HER2 amplified disease. Identification of miRs responsible for resistance to HER2 inhibitors may allow us to develop a novel, reproducible, non-invasive and cost-effective tool for GOC patient stratification. Defining predictive biomarkers of resistance to HER2 inhibitors would enable patient selection, minimise chances of severe toxicity in those less likely to respond, and may define novel strategies to restore drug sensitivity.

**Methods:** A high-throughput large-scale RNA interference screen in the HER2-amplified GOC cell line NCI-N87 and the HER2 non-amplified cell line FLO-1 was performed in order to discover novel miRs involved in sensitivity and resistance to trastuzumab. Cells were transfected using a library of 1015 miR mimics, control miRs and siPK1 positive control. They were treated 48 hours later with cisplatin + 5FU + trastuzumab based on IC50 data previously obtained. Cell viability was analysed after 72 hrs of continuous drug treatment by fluorescence-based (Cell Titer Blue® and EnVision™). Data from 3 biological replicates was analysed and shortlisting of significant hits was based on the concordance among data from different replicates. miRs were considered significant if they caused >40% decrease in cell viability with a t-test p value of <0.001.

**Results:** Thirty-two miRs caused >40% decrease in cell viability and were associated with a p value of <0.001 in the NCI-N87 cell line. Forty-six miRs caused >40% decrease in cell viability and were associated with a p value of <0.001 between replicates in the FLO-1 cell line. Eight miRs were concordant between the two cell lines.

**Conclusions:** We identified a panel of miRs associated with GOC resistance to HER2 inhibitors in combination with chemotherapy. Inhibition of these miRs significantly affects GOC cell viability and restores sensitivity to HER2 inhibitors plus chemotherapy. These miRs require validation with Ixapon miR inhibitors and Nanostring analysis. Translational studies will be conducted in the ST03 HER2 substudy (EUDRACT 2006-000811-12).

**Legal entity responsible for the study:** National Cancer Research UK

**Disclosure:** D. Cunningham: Institution has received research funding from AstraZeneca, Amgen, Celgene, Merck Serono, Sanofi, Merrimack, and Medimmune. All other authors have declared no conflicts of interest.

## 1596P miR-7 modulates pancreatic cancer progression by interfering with aerobic glycolysis via inhibition of autophagy

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**Background:** Pancreatic cancers have abnormally high basal autophagy even under fed conditions, and are commonly addicted to aerobic glycolysis for survival and growth. This suggests that oncogenic events create inherent metabolic stress necessitating autophagy activation to sustain tumor cell survival. Thus, autophagy inhibition may exert the potential of antitumor. Recently, we and others described miR-7 acted as a tumor suppressor. However, the role of miR-7 in the context of pancreatic ductal adenocarcinoma (PDAC) remains unknown. Here, we investigated the biological functions of miR-7 in PDAC, and explored the underlying mechanism of miR-7 regulatory network related to autophagy and aerobic glycolysis.

**Methods:** The level of intracellular glucose, LDH activity and lactate production were detected by corresponding kits. A dual-luciferase reporter assay system was used to determine miR-7 target genes.

**Results:** Inhibition of autophagy by hydroxymethylglutaryl-CoA reductase could down-regulate the intracellular glucose levels, LDH activity and lactate. In contrast, induction of autophagy by glucose or serum starvation, could increase the level of glycolysis. These findings indicated that pancreatic cancer cells made use of autophagy as a survival strategy to provide essential glucose required for glycolysis. Importantly, overexpression of miR-7 inhibited the level of Torin-1 or starvation-induced autophagy, intracellular glucose and glycolytic metabolism. c-ras-7, a sponge of miR-7, could enhance autophagy and increase glucose. To address the underlying mechanism, we explored the pathway of autophagy, glycolysis and their related signaling. Intriguingly, miR-7 repressed autophagy through suppressing LKB1, ULK2, ATG4A and ATG7 to reduce the intracellular glucose supply to glycolysis in PDAC. Furthermore, we demonstrated that miR-7 inhibited pancreatic cancer cell growth and metastasis in vitro and in vivo.

**Conclusions:** These findings indicate that miR-7 acts as a tumor suppressor in PDAC and is a crucial regulator in autophagy-derived pools of glucose to suppress PDAC progress. Thus, exogenous overexpression of miR-7 might be a promising strategy for PDAC treatment by targeting autophagy.

**Legal entity responsible for the study:** Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

**Funding:** The National Science Foundation of China

**Disclosure:** All authors have declared no conflicts of interest.

## 1597T Hepatoma cell functions modulated by NEK2 are associated with liver cancer progression

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**Background:** NEK2 (NIMA-related expressed kinase 2) is a serine/threonine centrosomal kinase that acts as a critical regulator of centrosome structure and function. aberrant NEK2 activities lead to failure in regulating centrosome duplication. An earlier functional study revealed that NEK2 mediates drug resistance via expression of an ABC10 transporter. Active angiogenesis and metastasis underlie the rapid recurrence and poor survival of HCC. However, the precise roles and mechanisms of NEK2 in liver cancer progression remain largely unknown.

**Methods:** NEK2 expression was assessed by real-time qRT-PCR. The function of NEK2 was determined by over-expression or depletion of the gene. In vivo matrigel plug angiogenesis assay was used to determine the influence of NEK2.

**Results:** NEK2 overexpression promotes tumorigenesis and is associated with poor prognosis in several cancers. Increased NEK2 expression during the late pathological stage has been detected in the Oncomine liver dataset and hepatocellular carcinoma (HCC) specimens. Elevated NEK2 protein is associated with poor overall survival in patients with HCC. Results from the current study showed that NEK2 mediates tumor metastasis and angiogenesis in vivo. NEK2-mediated drug resistance was blocked by a specific PI3K inhibitor. Moreover, NEK2 mediated liver cancer cell migration via pAKT/NF-κB signaling and matrix metalloproteinase (MMP) activation. Angiogenesis was induced via the same signaling pathway and IL-8 stimulation.
Conclusions: Our findings collectively indicate that NEK2 modulates hepatoma cell functions, including growth, drug resistance, metastasis and angiogenesis.

Legal entity responsible for the study: N/A
Funding: Chang-Gung Memorial Hospital, Taiwan
Disclosure: All authors have declared no conflicts of interest.

Characteristics and prognostic potential of tertiary lymphoid structures in oral tongue squamous cell carcinoma


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Background: Recently, tertiary lymphoid structures (TLSs) have been reported in melanoma, NSCLC, breast cancer, colorectal cancer and so on. They are considered to drive local adaptive immune responses against tumors and considered as important sites of extranodal T cell priming and epitope spreading in the responder T cell repertoire. In terms of prognostic value, TLS is the factory for immune response. Therefore TLS acts as a favorable clinical outcome for patients. But TLS was seldom reported on oral tongue squamous cell carcinoma. To identify and evaluate the presence of tertiary lymphoid structures in oral tongue squamous cell carcinomas (OTSCC). If present, we would study the prognostic values of TLSs in OTSCC and analyze whether they are related to the survival of OTSCC.

Methods: The expression of PNA+ HEV, CD20+ B cells, CD3+ T cells was examined to record the quantity of TLSs, using immunohistochemistry (IHC) in paraffin-embedded tissue samples from 168 OTSCC patients. Overall Survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method, with a log-rank test to compare the survival of groups with or without TLSs. The Mann-Whitney U test was used for univariate analysis with the Cox proportional hazards model. Variables that were statistically significant in the univariate analysis were entered into multivariate Cox regression analyses to identify its independent value.

Results: TLS was a well-organized structure composed of a specific indicator of HEV and distinct B cell aggregates and T cell area. TLSs were found in about 26.5% of OTSCC patients. Among clinicopathological data [including gender, age, smoking history, alcohol consumption, tumor differentiation, TNM stage and TLSs (tumor infiltrating lymphocyte)], TLSs were associated with TILs (p < 0.05). Log-rank test showed that presence of TLS affect the relapse and 5 year overall survival rates of OTSCC (both p < 0.05). In multivariate analyses, TLS was the independent factor of relapse and 5 year overall survival rates of OTSCC (both p < 0.05).

Conclusions: The presence of TLS in OTSCC was identified. TLS is associated with adverse prognosis in patients with OTSCC. It may play important roles in preventing the recurrence of OTSCC.

Legal entity responsible for the study: Guanghua School of Stomatolgy, Hospital of Stomatolgy, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Stomatolgy.
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Disclosure: All authors have declared no conflicts of interest.

Management optimization of non small cell lung cancer (NSCLC) specimens. A single institution experience with a multiplexed mass spectrometry approach

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Background: The development of targeted therapy has led to the need for subtyping of non-small cell lung carcinomas (NSCLC). The aim of this study was to assess the utility of immunohistochemical (IHC) markers in subtyping particularly poorly differentiated NSCLC in small biopsy specimens and also investigate NSCLC for enteric differentiation.

Methods: At total of 760 small lung biopsies diagnosed as NSCLC between 2001-2011 were re-evaluated for tumor typing morphologically. Among these, 126 cases (108 NSCLC-not otherwise specified (NOS), 11 squamous cell carcinoma (SCC), 7 adenoscarcinoma (ADC) and 1 adenosquamous carcinoma (AdSC)) were selected for IHC examination. These cases were classified for thyroid transcription factor-1 (TTF-1) + / Napsin A and p63 / CK5/6 stained and confirmed using the Kaplan-Aharon method, with a log-rank test. Multivariate survival analysis was done using the Cox proportional hazards model. Variables that were statistically significant in the univariate analysis were entered into multivariate Cox regression analyses to identify its independent value.

Results: For 366 (50.6%) of 724 cases diagnosed as NSCLC were morphologically typed and 358 (49.4%) of them were classified as NSCLC-NOS. After IHC examination, while 74 (69%) of 108 NSCLC-NOS cases could be typed, 34 (31%) of cases could not be classified in spite of IHC examination: TTF-1 expression in 100% of ADC and 7% of SCC, Napsin A expression in 77% of ADC and 2% of SCC, p63 expression in 93% of SCC and 28% of ADC, CK5/6 expression in 96% of SCC and 9% of ADC, DSG-3 expression in 21% of SCC and none of ADC and CK7 expression in 89% of ADC and 30% of SCC were observed. CKD2 positivity was detected in 14.3% of ADC, 17.9% of SCC and 29.4% of NSCLC-NOS cases. 5.6% of NSCLC-NOS cases expressed CK20. Diagnostic concordance compared between biopsy and resection specimens in 40 cases was found to be 65% (100% with respect to SCC).

Conclusions: A panel of TTF-1, p63 and CK5/6 allows to reliably classify 70% of poorly differentiated NSCLC cases in small biopsy specimens.

Legal entity responsible for the study: N/A
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Disclosure: All authors have declared no conflicts of interest.

Genomic DNA from HT29 cells and its modified forms influence in vitro survival of the same tumor cells via TLR9- and autophagy signaling

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Background: The interleukin-related role of TLR9 and autophagy signaling in cancer has not yet been clarified. In our previous study incubation of HT29 cancer cells with modified self-DNAs resulted in different effects on TLR9-signaling and cell differentiation. This study was designed to assess the TLR9-related activities of self-DNA sequences on cell survival and autophagy response in HT29 cells.

Methods: HT29 cells were incubated with 72 different self-DNA sequences with intact genomic (g), artifically hypermethylated (m), fragmented (f), and hypermethylated/fragmented (m/f) tumoral self-DNAs. Cell viability was measured by MTT assay, while induction of apoptosis by TUNEL. Cell proliferation was estimated by Ki67 immunocytochemistry. Transcriptional changes of TLR9- and autophagy pathways were assayed by qRT-PCR and immunocytochemistry. Morphologic features of apoptosis and autophagy were
examined by transmission electron microscopy (TEM). The number of desmosome-positive wells was also determined.

**Results:** Following incubation with g-, m-, and mainly with m-DNAs viability and proliferation rate of HT29 cells decreased, while percentage of apoptotic cells increased. F-DNA resulted in an enhanced cell survival on IL8 mRNA levels (Cmax) were reached at 2-6.7 hours post-dosing. After Tmax, the plasma concentrations decreased in a dose-proportional manner. The maximum concentration (Cmax) at dose levels of 25, 75 and 150 mg/kg. Study parameters compared pretreatment as well as day 29 (main and recovery animals) and day 55 (recovery animals). Blood was collected days 1 and 27 at 8 time points for toxicokinetics.

**Conclusions:** Preclinical animal data of the SM88 tyrosine isomer showed that the systemic exposures to tyrosine generally increased dose-dependently, and in a slightly less than dose-proportional manner. The maximum concentration levels (Cmax) were reached at 2-6.7 hours post-dosing. After Tmax, the plasma concentrations decreased in a dose-proportional manner. The maximum concentration levels (Cmax) at dose levels of 25, 75 and 150 mg/kg. Study parameters compared pretreatment as well as day 29 (main and recovery animals) and day 55 (recovery animals). Blood was collected days 1 and 27 at 8 time points for toxicokinetics.

**Results:** All animals demonstrated consistent organ and cell volume decrease and reversible upon discontinuation of the SM88 agent. There were no changes: in other organ weights, body weight, food consumption, ECGs, ophthalmic findings, hematology, coagulation, clinical chemistry/urinalysis, and no macroscopic or microscopic findings that could be attributed to the tyrosine at up to 150 mg/kg. Consequently the No Observed Effect Level (NOEL) was determined to be 150 mg/kg. Day 27 plasma Cmax values at 150 mg/kg were 41.7 ug/ml and 41.6 ug/ml for males and females respectively. AUC(0-t) values were 717.7 (males) and 724.8 (females) hr*ug/ml. The difference in combined tyrosine isomer concentrations in plasma between Day 1 and 27, show that the systemic exposures to tyrosine generally increased dose-dependently, and in a slightly less than dose-proportional manner. The maximum concentration levels (Cmax) were reached at 2-6.7 hours post-dosing. After Tmax, the plasma concentrations decreased gradually at a mean estimated Tmax value of 7.9-9.3 hrs on Day 1 and from 8.4-9.6 hrs on Day 27. There were no sex-related differences with sex ratios between 0.3 and 1.8 for all measured parameters. Over the 4-week treatment period, AUC(0-t) and AUC(0-t) (Cmax) accumulation ratios (Day 27/Day 1) ranged from 0.6-1.8 (0.8 to 1.6) with 25, 75 and 150 mg/kg, suggesting no accumulation when administered three (3) times per week over a 27 day period.

**Conclusions:** Pancreas changes suggest possible mechanisms and therapeutic insights to explain SM88’s clinical activity, supporting clinical trials.
Abemaciclib: 371P
ACT (Adoptive cell therapy): 326PD
Afatinib: 280P
Alectinib: 1407P
Alectinib: 1209PfD, 1263P, 1290TiP
Alisertib (MLN8237, aurora A kinase inhibitor): LBA29, 1423O, 1424O
ALK inhibitor: 1209Pf, 1263P, 1290TiP
AML201 (2-amino acid peptide derived from FKBP12): 1437P
Anti-akt inhibitor: 333P, 375P, 780P
Alpelisib (BYL719): 311TiP, 375P
ALW-114: 27O
AMRT01 (PEGylated human IL-1): 364PD
Amrubicin: 448P
Anamorelin (ONO-7643): 1434O, 1446P
ANG0015 (tau-selective derivative): 324O
Anastrozole: LBA39, LBA41, LBA48, LBA55, 209P
Androzole: LBA51, LBA57, LBA60, 1260P, 1267P, 1275P
Anti-CD20 monoclonal antibody therapy: 9457P
Anti-coagulase: 1479P
Anti-CTLA-4: LBA36, 846TIP, 1120P, 1130P
Anti-estrogen: 1280P
Anti-infectives: 1220P
Anti-metabolites: 1073P
Anti-microtubule agents: 1073P
Anti-neoplastic agents: 865P, 869P, 923P, 12080P

Bicalutamide: 1562P
Camptothecin: 389P, 864P
Carfilzomib: 929P, 941TI
Carnitine: 1467P
Caspofungin: 1303P
Cava21 (CavataK, immunotherapeutic strain of Coxsackievirus A21): 1051PD, 1054PD, 1104TP, 1117P
CD13: 943TP, 9457TP, 1048O
Cea-IL2 (Rg7813; cregurtuzum abnineaucleate): 3580C
Celzidrin: 328P, 1408P
Ceritinib: LBA42, PR, 410TP, 1205PD, 1280O, 1273P
Cell-11 (PD-targeting antibody): 1074P
Clenidoside: 328PD
Chlorambucil: 1467P
chemotherapy

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1128P, 1130P, 1131P, 1132P, 1134P, 1142P,
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