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## SUMMARY

The European Cancer Congress (ECC 2015) combined the 40th European Society for Medical Oncology (ESMO) congress with the 18th congress of the European Cancer Organisation (ECCO) and was held 25 to 29 September, 2015. The meeting was organised in partnership with the European Society of Radiation and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Academy for Cancer Research (EACR), the European Oncology Nursing Society (EONS), and International Society of Paediatric Oncology (SIOPE). The efforts of all partner organisations were united to continue advancing multidisciplinary as the way forward to optimise the prevention, diagnosis, treatment, and care of cancer patients by encouraging participants to leverage knowledge, promote education and build awareness for patient-centred oncology.

## INTRODUCTION

The comprehensive scientific programme was designed by experts in oncology to provide topics of widespread multidisciplinary and multiprofessional interest. The programme offered new research, up to date educational symposia, and state of the science teaching lectures. The far-reaching scientific tracks covered diverse aspects of medical oncology, with investigators coming from around the world to share the latest data, which often contributed to the development of an unprecedented number of new treatments. Many educational programmes were held that maintained the position of the ECC as the largest continuing medical education accredited event in Europe in 2015.

ECC 2015 combined the efforts of the leading organisations, scientists, and practitioners in the field of cancer with the aim of improving the prevention, diagnosis, treatment, and care of cancer patients. ECC 2015 gave not just a European, but also, a global overview of the field of cancer with the aim that participants could leave the congress with a comprehensive understanding of current issues and novel treatments, and also a renewed dedication to provide the best possible medical care for all patients.

A brief summary of some of the diverse scientific findings presented during the ECC 2015 follows.

## BASIC SCIENCE

### Combined inhibition of IGF1R and EGFR signalling overcomes the resistance to third-generation EGFR kinase inhibitors due to IGF1R activation in cell lines

Sun Cheol Park, Asan Medical Center, Pulmonology and Critical Care Medicine, Seoul, Korea and colleagues investigated the mechanism behind the loss of clinical efficacy due to the development of resistance to the highly effective third generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Since third generation of EGFR-TKIs are known to control growth in lung cancer cells with T790M-mediated resistance, the investigators used PC-9/GR cells, which contain both EGFR exon 19 deletions and T790M mutations, to develop cell sublines (the PC-9/GR/WR cell line), that are also resistant to WZ4002 (a third generation EGFR TKI). They also blocked IGF1R signaling with AG1024 (a small molecule IGF1R inhibitor) and then used a multi-kinase assay to determine the activation of a bypass signal.

In their assay, the subline PC-9/GR/WR demonstrated cross-resistance to other third generation EGFR-TKIs, including AZD9291 and CO1686 but WZ4002 was unable to inhibit the growth of cancer cells despite the effective suppression of EGFR activation. EGFR down-regulation by small hairpin RNA (shRNA) also could not control cancer cell proliferation, suggesting the activation of a bypass growth signal. The PC-9/GR/WR cells showed activation of IGF1R plus IGFBP3 loss, which suggested that the down-regulation of IGF1R by shRNA and the inhibition of IGF1R signal by AG1024 could restore WZ4002. Park et al. Abstract 101.

#### Practice point and future research opportunities

Strategies to overcome resistance to third generation of EGFR-TKIs is an important therapeutic goal; this team has made a significant step forward by identifying a possible mechanism of IGF1R activation accompanied by IGFBP3 loss and postulating the combined inhibition of IGF1R plus EGFR signalling could restore sensitivity to WZ4002.

### Combination treatment with a tyrosine kinase inhibitor plus an IL-6 receptor antibody assessed in renal cell carcinoma cell lines and mice

According to findings presented by Kei Ishibashi, Fukushima Medical University, Fukushima, Japan, treatment with TKIs against the vascular endothelial growth factor (VEGF) pathways, which



represents the current standard of care in advanced renal cell carcinoma (RCC), activates the interleukin-6 (IL-6) signalling pathway, and induces IL-6, suggesting that activity with these TKIs may be improved by adding an IL-6 agonist such as the humanised monoclonal antibody to the IL-6 receptor, tocilizumab.

Human RCC cell lines 786-O, Caki-2, CCF-RC1 and A498 were treated in this study with the TKIs sorafenib and sunitinib at concentrations of 0.5, 1.0, 5.0, 10.0  $\mu$ M. Following this treatment, the 786-O RCC cell line secreted IL-6 and VEGF, as measured by the VersaMAP Development System. Western blot analyses revealed that Akt and mTOR were activated by TKI treatment even at the lowest concentration of 0.5 mM. HIF2a expression and the phosphorylation of NFkB were also demonstrated by Western blot; these changes are linked to VEGF and IL-6 expression. Analysis of the IL-6 signaling pathway using an IL-6R antibody, the MTT assay and Western blot, showed that tocilizumab treatment plus TKIs could reduce the activation of the IL-6 signaling pathway and also suppressed cell proliferation.

The mean SUVmax indicating tumour viability was compared in athymic mice receiving tocilizumab plus sorafenib with similar mice receiving sorafenib and was found to be decreased in athymic mice receiving combination therapy; the mean SUVmax was  $9.8 \pm 1.6$  compared with  $11.5 \pm 0.8$ , respectively ( $p = 0.04$ ). The investigators also noted that the areas of necrosis in the tumours were significantly increased ( $206 \pm 56 \text{ mm}^3$ ) in mice receiving the combination compared with similar areas in tumours of mice receiving sole sorafenib ( $117 \pm 31 \text{ mm}^3$ ;  $p = 0.02$ ). CD31 expression was also reduced with tocilizumab plus sorafenib compared with sorafenib alone. The investigators concluded that TKIs induce IL-6 secretion in RCC cells, leading to VEGF secretion, angiogenesis, and increased cell proliferation. Ishibashi et al. Abstract 102.

### Practice point and future research opportunities

These results suggest that co-administration of an IL-6 antibody with TKIs decreases angiogenesis and cell proliferation in renal cell carcinoma cells in vitro and in mice, warranting further investigation.

**Subtype of CDH2 negative oesophageal squamous cell carcinoma with cytotoxic T-lymphocyte signatures shows a good response to definitive chemoradiotherapy**



A team led by Yashuhito Tanaka, Nagoya City University Hospital, Nagoya, Japan previously reported that tumour-specific cytotoxic T-lymphocyte (CTL) activation signatures were preferentially found in long-term survivors after definitive chemoradiotherapy (dCRT). In the study presented at the ECC, the investigators sought to determine whether CRT actually drives the CTL activation by evaluating the effect of CRT on tumour tissues. Expression profiles of needle biopsy specimens obtained from 30 patients with oesophageal squamous cell carcinoma before and after treatment were created by gene expression profiling, using oligonucleotide microarrays. The specimens included 19 complete response (CR) and 11 non-CR cases. Gene expression profiles were also obtained from another 125 samples, with survival analysis performed in 121 of the 125 cases where clinical data was available.

The investigators found the post-treatment samples from the 19 CR cases contained 1014 up-regulated genes, including at least 240 tumour-specific CTL-activation associated genes including IFNG, PRF1, and GZMB. The expression profiles of these 240 tumour specific genes could distinguish immune-activated cases, from other cases. Although the CR rate was better in the immune-activated gene cases, no association with overall survival (OS) was found in the 30 patient samples or in the additional 125 samples.

A comparison of expression profiles between cases with and without early relapse identified a series of epithelial to mesenchymal transition-related genes that were over-expressed in early relapse cases. Since it had been shown that the intestinal-type with epithelial characteristics and the diffuse-type with mesenchymal characteristics of oesophageal squamous cell carcinoma could be distinguished by the ratio of CDH1 and CDH2 in gastric cancer, the investigators applied this ratio to the oesophageal cancer analysis, which showed that OS in CDH2 negative cases was significantly better than in CDH2 positive cases ( $p = 0.012$ ). Furthermore, the 5-year survival was 56% versus 20% in CDH2 negative versus CDH2 positive cases, respectively. The clinical outcome, represented by the OS and recurrence rates, associated with the immune-activated gene cases; the outcome of CDH2-negative cases was significantly better than that of CDH2-positive cases ( $p = 0.012$ ). The 5-year survival rate was 73% versus 7%, respectively in the immune-activated gene cases. Tanaka et al. Abstract 104.

### **Practice point and future research opportunities**

This analysis identifies genes, crucially many immune-related genes, that are upregulated after dCRT treatment of oesophageal squamous cell carcinoma and also shows an association between

a phenotype that is CDH2 negative with cytotoxic T-lymphocyte signatures and improved clinical benefit from dCRT.

## TRANSLATIONAL RESEARCH

### High frequency of potentially targetable ERBB2 extracellular domain mutations detected in multiple cancer types by comprehensive genomic profiling

Lead author Jeffrey Ross, Pathology Department, Medical Centre, Albany, USA and Medical Director of Foundation Medicine, Inc., Cambridge, USA, presented findings from comprehensive genomic profiling (CGP) of a large series of tumour samples that determined the incidence of mutations within the extracellular domains (ECD) of ERBB2 that can be targeted by existing anti-HER2 therapies. Most oncogenic mutations in the ECD are generally mutually exclusive of ERBB2 amplifications and occur in a wide variety of human cancers. Most ERBB2 ECD mutations involve S310F and S310Y base substitutions; recent reports have linked tumours having these genomic alterations with good responses to anti-HER2 targeted therapies, including currently available kinase inhibitors and antibodies.

CGP was done on 37,772 clinical FFPE cancer samples using hybridisation capture of exonic regions from 315 cancer-related genes and select introns from 19 genes commonly rearranged in cancer. The investigators used  $\geq 50$  ng samples of DNA, which were extracted and sequenced to high, uniform median coverage (623X) to identify clinically relevant genomic alterations (CRGA), defined as sequences that correspond to targets of existing anti-cancer drugs that are either on the market or being used in registered clinical trials.

CGP revealed that S310F or S310Y ERBB2 ECD mutations occurred in 177 (0.5%) of the 37,772 clinical samples that were sequenced, while just 34 (0.01%) non-ECD ERBB2 point mutations were identified in this series. The majority (76%) of the ERBB2 ECD mutations were confined to 7 tumour types, including bladder/kidney urothelial carcinoma (UC), carcinoma of unknown primary (CUP), biliary tract carcinoma (BTC), lung cancer, colorectal carcinoma, breast cancer, and gastroesophageal carcinoma. The incidence of ERBB2 ECD extracellular domain alterations was significant compared to other tumour types: Incidence was 18% in both UC and CUP with mutations occurring in 3.20% ( $p < 0.0001$ ) and in 0.96% of tumours, respectively, ( $p = 0.00049$ ), and 7% in BTC, where it was present in 1.10% of tumours ( $p = 0.0045$ ).

ERBB2 ECD mutation was also highly associated with the micropapillary variant of UC compared to conventional UC ( $p < 0.0001$ ). More than 30 other tumour types accounted for the remaining 24% of the ERBB2 ECD mutations identified.

Tumour Type	Tumours with <i>ERBB2</i> ECD Mutations			
	Total Cases	% of Total <i>ERBB2</i> ECD Mutations	% in this Tumour Type	Comparison of this Tumour Type to All Tumour Types
Bladder/Kidney Urothelial Carcinoma (UC)	32	18%	3.20%	$P < 0.0001$
Unknown Primary Carcinoma (CUP)	32	18%	0.96%	$P = 0.0004$
Lung Carcinoma	22	12%	0.35%	NS
Breast Carcinoma	14	8%	0.26%	NS
Biliary Tract Carcinoma (BTC)	13	7%	1.10%	$P = 0.0045$
Gastroesophageal Carcinoma	12	7%	0.71%	NS
Colorectal Carcinoma	10	6%	0.19%	NS

**Caption:** Frequency of Targetable *ERBB2* Extra-Cellular Domain (ECD) Mutations across Multiple Tumour Types

**Credit:** Jeffrey Ross

CGP detected genomic sequence alterations that are not detectable by IHC and FISH and thus are missed when *ERBB2* status is determined by conventional methods; normal *ERBB2* copy number was detected in 154 (87%) of the *ERBB2* ECD mutated cancers and, therefore, would not have been identified as *ERBB2* “positive” by FISH or IHC testing. The authors emphasised that, although *ERBB2* ECD mutations are rare, they represent important targetable genomic alterations

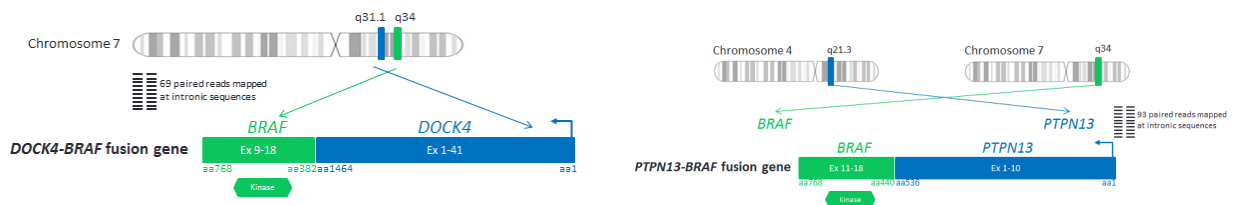
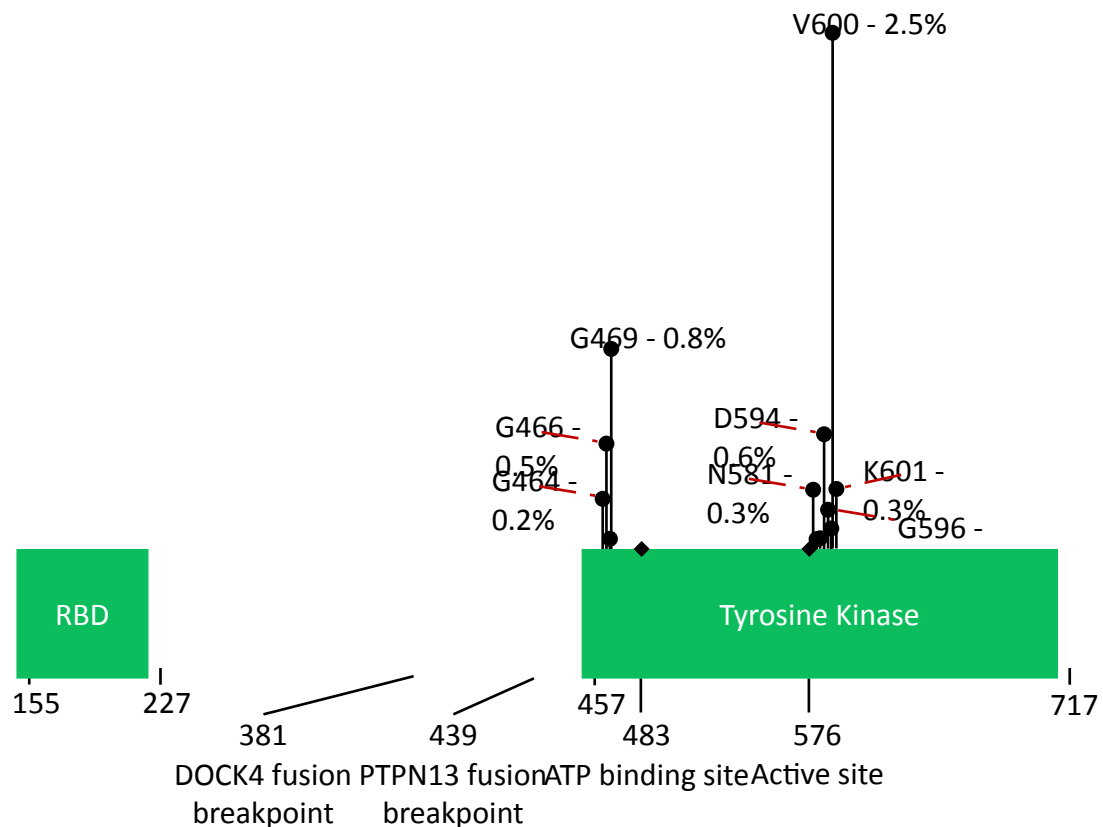
occurring across a wide range of tumour types and are enriched in specific tumours. Ross et al. Abstract P144.

### Practice point and future research opportunities

Therapeutically relevant extracellular domain mutations in ERBB2/HER2 were observed across multiple tumour types that may show good responses to already existing anti-HER2 targeted therapies. These ERBB2 sequence alterations remain undetectable by other modalities, and represent the utility of comprehensive genomic profiling to personalise treatment for patients with advanced and refractory malignancies.

### Comprehensive genomic profiling of BRAF in a large series of lung cancer samples

Siraj Ali, Foundation Medicine, Inc., Cambridge, USA discussed the incidence of molecular alterations in the BRAF gene derived from analysis of 3300 consecutive lung cancer samples using next generation sequencing (NGS). He reported results from a large-scale genomic evaluation that reviewed biopsies that were obtained in the course of clinical care for alterations thought to activate BRAF using comprehensive genomic profiling (CGP). In all, 2179 lung adenocarcinoma (LADCA) samples, 535 non-squamous non-small cell lung cancer (NSCLC), 385 squamous cell cancer (SCC), and 201 small-cell lung cancer (SCLC) tumour samples were analysed. DNA was extracted from 40 microns of FFPE and CGP was performed on hybridisation-captured, adaptor ligation based libraries to a mean coverage depth of >500X for 3,769 exons of 315 cancer-related genes plus selected introns from 28 genes that are known to be frequently rearranged in cancer. The results were evaluated for all classes of genomic alterations. Clinically relevant genomic alterations (CRGA) were defined as genomic alterations linked to the response to drugs already on the market or under evaluation in clinical trials.



**Caption:** BRAF genomic alterations in 2179 case of lung adenocarcinoma assayed by genomic profiling in the course of clinical care (mutation: frequency).

**Credit:** Siraj Ali

The oncogenic BRAF alterations identified included mutation, fusion, and amplification. Mutations were most commonly detected in 5.5% of LADCA, 3.0% of non-squamous NSCLC, and in 0.8% of SCC samples, but not in SCLC, which had the smallest sample size of 201 cases. Previous reports

estimate that BRAF V600E driver mutations are found in approximately 2-3% of patients with NSCLC and are generally mutually exclusive of other oncogenic drivers. BRAF V600 was the most frequently occurring mutation in this series and was detected in 2.5% of LADCA and 0.4% of non-squamous NSCLC samples. In addition to V600E, a subset of other BRAF genetic alterations, including certain fusions, may also be oncogenic as they activate either the kinase domain or downstream targets; other alterations more frequently identified were G469 in 0.8% versus 1.3%, G466 at 0.5% versus 0.6%, and D594 at 0.6% versus 0.0% of LADCA and non-squamous NSCLC samples, respectively. Alterations in BRAF G469 and D594 were detected in 0.3% of SCC samples. Alterations occurring in less than 0.5% of tumour types included G464, N581, and K601. Two LADCA samples harboured novel fusions, DOCK4-BRAF and PTPN13-BRAF; of these, one patient developed acquired resistance to vemurafenib, but response was restored with the addition of everolimus.

The authors summarised that CGP can be used successfully to identify all classes of BRAF alterations in NSCLC, which reached nearly a 5% frequency of alteration. The rates of specific alterations differed between histologic subtypes, with approximately 50% of BRAF V600E mutations seen in LADCA compared to non-squamous NSCLC, where just 12.5% of BRAF V600E alterations were detected but contained 87.5% of intermediately activating BRAF alterations. They suggest that limited benefit can be obtained from BRAF testing in SCLC wherein no BRAF alterations were found and possibly SCC, where less than 1% of samples contained BRAF mutations. They also suggested that patients with NSCLC harbouring other activating alterations of BRAF may also benefit from treatment from BRAF V600E inhibitors in ongoing NSCLC clinical trials. Ali et al. Abstract 3007.

### Practice point and future research opportunities

BRAF is a key component of the RAS-RAF-MEK-ERK signalling pathway, an important component of the downstream molecular network activated by a number of receptor tyrosine kinases, that provides the oncogenic potential for aberrant signalling in this pathway. BRAF activation by a number of molecular mechanisms is one way the pathway may be activated in cancer. Mutations reported in this study include those substitution mutations at position 600, the commonest of which is V600E, which activate the BRAF kinase and are oncogenic in vitro; the physiological effect of the non-V600 mutations is much less clear. The finding of BRAF fusion is interesting but a rare phenomenon. The distribution of mutations by histology is discussed but few data exist with which to compare these results. The few reports of BRAF mutation in squamous cell carcinoma tend to



be non-V600 mutations; with limited comparators, it is difficult to draw any conclusion regarding the dominance of non-V600 mutations in the non-squamous NSCLC group.

The NGS approach in this study has presumably generated data that will be of interest. Mutation prevalence data may be confounded by the technology used to find the mutations if it is allele specific, which is not an issue in this study and the population studied, where there is case selection, especially when there is uneven distribution of mutations by histology.

## BREAST CANCER

### Study supports omitting a re-excision for a focally positive surgical margin after primary breast conserving surgery

Lead investigator Elvira Vos, Erasmus MC Cancer Institute, Rotterdam, The Netherlands reported on the ipsilateral breast tumour recurrence (IBTR) overall survival of patients with invasive breast cancer patients after primary breast conserving surgery (BCS) followed by re-excision compared with patients having primary BCS only. Dutch national guidelines in place since 2002 recommend reserving re-excision for invasive tumours showing a 'more than focally positive' margin, which was defined as the foci of tumour touching ink, but over a length of <4mm. Noting that Dutch re-excision indications are less stringent compared with Society of Surgical Oncology-American Society for Radiation Oncology guideline, the investigators conducted a retrospective analyses of data from a Dutch registry of 35,261 women, aged less than 75 years with unilateral invasive breast cancer, stage pT1–T3 but no prior malignancy, that were treated by BCS and radiotherapy between 1999 and 2012. Patients without information about margin status or incomplete follow-up were excluded.

Information on margin status and follow-up was available in 7,940 patients who were placed into cohorts based upon 'primary BCS only', 're-excision by BCS', and 're-excision by mastectomy'. Univariable and multivariable Cox regression analyses were performed that adjusted for clinicopathological characteristics, including age, histology, differentiation grade, tumour status, regional lymph node status, oestrogen-, progesterone-and HER2 receptor status, chemotherapy and hormonal therapy use. Median time of follow-up was 87 (interquartile range 65 to 120) months. Negative margins were found in 5,887 (74.1%) patients, 'focally positive' margins in 831 (10.5%), and 'more than focally positive' margins were found in 1222 (15.4%) patients. No association was found between margin status and the occurrence of IBTR, odds ratio (OR) 1.04; 95% CI 0.89, 1.20). IBTR was reported in 171 (2.9%) women with negative margins, and in 22 (2.6%) women with focally positive margins; 52 (4.3%) women with more than focally positive margins showed an elevated rate of IBTR that did not reach statistical significance ( $p = 0.034$ ).

Importantly, in the cohort wherein treatment was carried out in 365 (43.9%) patients having a 'focally positive' margin per Dutch guidelines, specifically no re-excision, no significant association with IBTR was observed (unadjusted HR 1.40; 95%CI 0.61, 3.24; adjusted HR 1.54 95%CI 0.64,

3.74). This cohort also showed no association with disease-free survival (unadjusted HR 1.02; 95%CI 0.70, 1.50) or with overall survival (unadjusted HR 1.09; 95% CI 0.74, 1.61). The authors concluded that omission of a re-excision for a focally positive surgical margin 87 months after primary BCS for invasive breast cancer does not seem to be associated with IBTR, disease-free survival, and overall survival. Vos et al. Abstract 1806.

### Practice point and future research opportunities

These data, though limited in numbers, support the Dutch guideline that considers it to be a safe procedure to omit a re-excision in patients having a focally positive margin after breast conserving surgery. Additional analyses would be needed to inform a review of overall guidelines.

### Predictors for pathological complete response with combined trastuzumab and lapatinib emerge from the NeoALTTO Trial

An analysis of gene signatures by RNA sequencing was conducted by Christos Sotiriou, Institut Jules Bordet, Brussels, Belgium and colleagues to identify the genes implicated in the response to combination trastuzumab/lapatinib plus weekly paclitaxel for HER2 positive early breast cancer. They used data from the phase III NeoALTTO trial, wherein the combination nearly doubled the rate of pathological complete response (pCR) over trastuzumab or lapatinib plus paclitaxel. The investigators identified clinically relevant genes in order to guide treatment. Of 455 patients enrolled in NeoALTTO, 254 patient baseline biopsies had RNA of sufficient quality and quantity. Random primed cDNA libraries were constructed and sequenced on the Illumina HiSeq 2000 platform in paired end mode. The gene sequences tested were related to proliferation, immune, stromal, AKT/mTOR and androgen receptor pathway activation. No significant differences in clinical parameters between the sequenced population and the main study population were observed. The relationship between pCR and the expression of several clinically and biologically relevant genes signatures (GS), as well as of the ERBB2 and ESR1 genes was assessed using logistic regressions.

The median sequencing depth was 54.7M read pairs. High ERBB2 expression associated the most strongly with pCR and was identified as the most significant predictor of pCR ( $p = 1.9e-08$ ), followed by low levels of ESR1 ( $p = 7.2e-05$ ), and expression of immune and proliferation-based signatures (GGI;  $p = 0.0065$ ). Multivariate analysis of combination treatment versus sole

trastuzumab or lapatinib showed the best model included ERBB2, ESR1 and an immune gene signature.

Analysis by treatment arm revealed that ERBB2 and ESR1 expression associated most strongly with pCR in the combination treatment arm but were also expressed in the monotherapy arms. The immune signatures were significant only in the combination trastuzumab plus lapatinib arm, which was confirmed with an interaction test ( $p = 0.0029$ , OR 3.4). No other signatures or genes were found to be a significant predictor of pCR independently of ESR1, ERBB2 and an immune gene signature. Sortiriou et al. Abstract 1811.

### Practice point and future research opportunities

NeoALTTO demonstrated that trastuzumab plus lapatinib was superior to either agent alone in achieving pCR in HER2 positive early breast cancer. RNA sequencing and multivariate analysis determined that high levels of ERBB2 and low levels of ESR1 associated with pCR in all treatment arms, but the association was strongest with combination treatment. High expression of immune genes associated with pCR only in the combination arm. These gene signatures may serve as predictors of pathological complete response and identify patients that are likely to benefit from combination trastuzumab plus lapatinib treatment.

### Discordance found between the HER2-phenotype on circulating tumour cells and the primary tumour in women with HER2 negative metastatic breast cancer

Wolfgang Janni, University Hospital Ulm, Ulm, Germany, presented findings on behalf of the DETECT study group from an interim analysis of the DETECT study, which was designed to evaluate the prognostic and predictive value of HER2-status of circulating tumour cells (CTCs) in patients with metastatic breast cancer (MBC). The study first assessed the prevalence of HER2 positive CTCs in patients with HER2 negative MBC, and then determined the association of the CTCs to the primary tumour and patient characteristics. CTCs were quantitated using the FDA-cleared CellSearch® System and HER2 status was evaluated in 1123 (as of April 2015) women with HER2-negative MBC. Patients were defined as CTC positive if at least 1 CTC was detected in 7.5 ml of peripheral blood, and as having a positive HER2-status on CTCs if at least 1 CTC with a strong (+++) immunocytochemical HER2 staining intensity was found.

CTCs were detected in 711 (63.3%) screened patients, who showed a median 7 CTCs (range: 1 to 35078). Of these CTC-positive patients, 139 (19.5%) had one CTC, 184 (25.9%) had 2 to 5 CTCs, 90 (12.7%) had 6 to 10 CTCs, 175 (24.6%) had 11 to 50 CTCs, and 123 (17.3%) had more than 50 CTCs. The presence of CTCs significantly associated with a higher proportion of pN2/pN3 tumours (28.3% versus 19.9%;  $p = 0.008$ ) and a higher proportion of lobular carcinomas (22.5% versus 9.5%;  $p < 0.001$ ). However, no association was found between CTCs and the grade ( $p = 0.326$ ) or hormone receptor status ( $p = 0.103$ ) of the primary tumour. In addition, the presence of CTCs was not associated with patient age ( $p = 0.313$ ), menopausal status at screening ( $p = 0.823$ ), or the time interval between primary diagnosis and screening ( $p = 0.992$ ).

At least one HER2-positive CTC was found in 134 (18.8%) of the patients with HER2-negative MBC and CTCs (median 2 HER2-positive CTCs; range: 1 to 80), indicating frequent HER2 status discordance between the primary tumour and CTCs. Of the patients with HER2-positive CTCs, 51 (38.1%) had one HER2-positive CTC, 48 (35.8%) had 2 to 5 HER2-positive CTCs, 15 (11.2%) had 6 to 10 HER2-positive CTCs, 16 (11.9%) had 11 to 50 HER2-positive CTCs, and 4 (3.0%) patients had more than 50 HER2-positive CTCs. The presence of HER2-positive CTCs was associated with hormone-receptor positive primary tumours, meaning that patients with triple-negative tumours were less likely to have HER2-positive CTCs than patients with HER2-negative but hormone-receptor positive tumours (6.1 versus 21.9%;  $p < 0.001$ ), respectively. The investigators are evaluating the efficacy of individualised breast cancer treatment based on the HER2 phenotype of CTCs in the randomised DETECT III trial. Janni et al. Abstract 1805.

### Practice point and future research opportunities

Findings from a large cohort of patients with HER2-negative MBC confirmed discordance in HER2 status between the primary tumour and CTCs in 18.8% of patients. Furthermore, the presence of HER2-positive CTCs was associated with hormone-receptor positive tumours. The results of the DETECT III trial should inform whether the phenotype of CTCs may be used to guide treatment in HER-2 negative breast cancer.

**TURANDOT: Overall survival analysis shows first-line bevacizumab plus capecitabine non-inferior to bevacizumab plus paclitaxel in locally recurrent metastatic breast cancer**

Thomas Brodowicz, Medical University Vienna in Vienna, Austria presented overall survival (OS) results from the open-label randomised phase III TURANDOT trial, which aimed to demonstrate non-inferior OS with first-line bevacizumab/capecitabine versus bevacizumab/paclitaxel in patients with locally recurrent/metastatic breast cancer (LR/MBC). Currently, bevacizumab/capecitabine and bevacizumab/paclitaxel regimens are approved by European regulatory authorities based on the superior progression-free survival (PFS) demonstrated with both of these regimens versus chemotherapy alone (Miller et al., NEJM 2007; Robert et al, JCO 2010). However, until now, the relative efficacy of these two regimens in terms of OS has remained unclear.

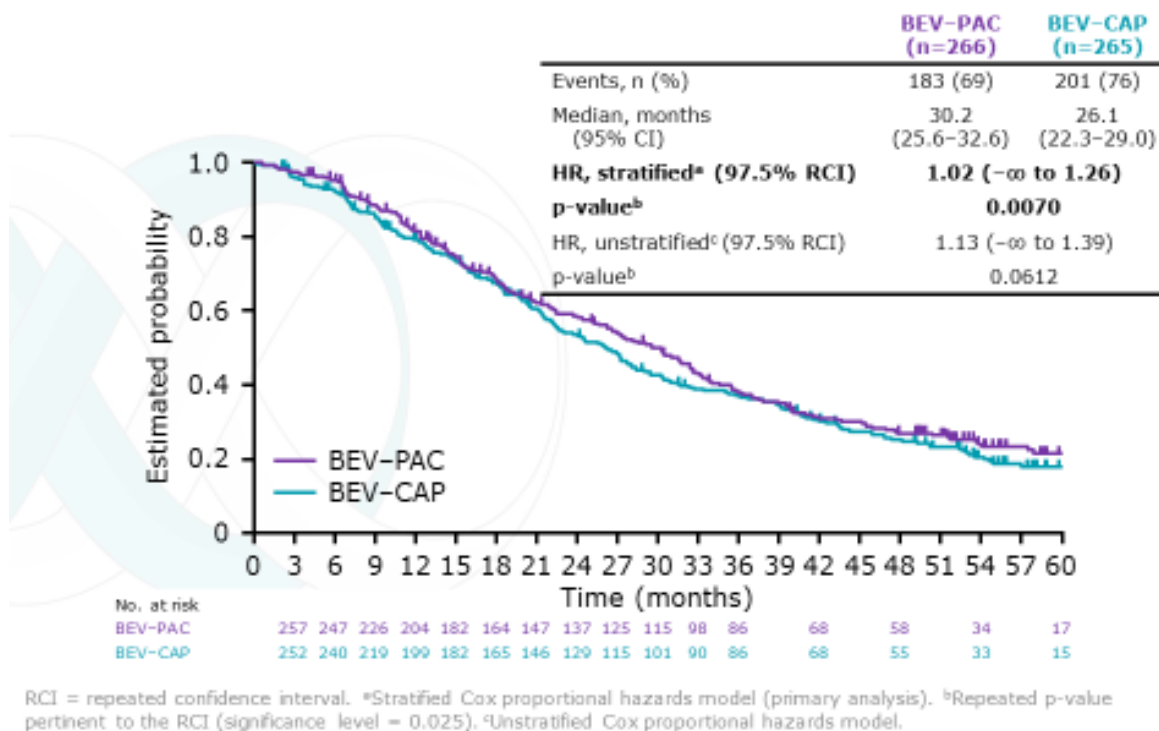
TURANDOT enrolled 564 patients from 51 centres in 12 countries. Eligible patients had HER2-negative LR/MBC and had received no prior chemotherapy for advanced disease. Patients were randomised to receive either bevacizumab/paclitaxel (intravenous (i.v.) bevacizumab at 10 mg/kg on days 1 and 15 plus i.v. paclitaxel at 90 mg/m<sup>2</sup> on days 1, 8 and 15, repeated every 4 weeks; n=285) or bevacizumab/capecitabine (i.v. bevacizumab at 15 mg/kg on day 1 plus oral capecitabine at 1000 mg/m<sup>2</sup> twice daily on days 1–14, repeated every 3 weeks; n=279) until disease progression or unacceptable toxic effects. The stratification factors were country, oestrogen/progesterone receptor status and menopausal status. The primary objective was to demonstrate non-inferior OS with first-line bevacizumab/capecitabine versus bevacizumab/paclitaxel by rejecting the null hypothesis of inferiority (HR  $\geq 1.33$ ) using a stratified Cox proportional hazard model. Sensitivity analyses were performed in the intent to treat (ITT) population and also using an unstratified Cox model in both populations. Subgroup analyses in clinically relevant populations were prespecified.

Whereas previously reported results of the interim analysis were inconclusive and non-inferior OS could not be demonstrated, the final results from TURANDOT demonstrated non-inferior OS in the bevacizumab/capecitabine arm compared with bevacizumab/paclitaxel in the primary stratified analysis in the per-protocol (PP) population, which was performed after 183 (69%) deaths occurred in 266 bevacizumab/paclitaxel patients and 201 (76%) in 265 patients in the bevacizumab/capecitabine arm. The stratified HR was 1.02 (97.5% repeated CI  $-\infty$  to 1.26; p = 0.007), meeting the criteria for non-inferiority and meeting the trial's primary objective. Median OS was 30.2 months in the bevacizumab/paclitaxel arm versus 26.1 months in the bevacizumab/capecitabine arm.

Results of the stratified ITT analysis were consistent with the PP results; however, results from stratified and unstratified analyses were inconsistent. The unstratified analysis in the PP population

showed HR 1.13 (97.5% repeated CI  $-\infty$ , 1.39). The PFS benefit with bevacizumab/paclitaxel over bevacizumab/capecitabine was supported by this final analysis, as was the superior objective response rate.

### Overall survival (per-protocol population, n=531)



**Caption:** Final results of the randomised phase III TURANDOT trial demonstrated non-inferior overall survival with bevacizumab plus capecitabine versus bevacizumab plus paclitaxel as first-line therapy for HER2-negative metastatic breast cancer in the primary analysis.

**Credit:** Christoph Zielinski

Subgroup analyses according to hormone receptor status, ECOG performance status, age, presence of visceral metastases and prior anthracycline and/or taxane therapy, showed no difference in OS between the treatment arms. However, in the subgroups of premenopausal females and patients with a body surface area  $\geq 1.8$  m<sup>2</sup>, OS appeared to be more favourable with



bevacizumab/paclitaxel than with bevacizumab/capecitabine. However, only 95 pre-menopausal patients were included in the subgroup, and the small sample size may have biased the data. The authors noted that, although the TURANDOT trial met its primary objective in the primary final OS analysis, there was inconsistency between the stratified and unstratified analyses and plan to explore this inconsistency, as well as the heterogeneity among subgroups. NCT00600340. Brodowicz et al. Abstract 1800.

### Practice point and future research opportunities

The inconsistency between stratified and unstratified results is under examination. This study shows that paclitaxel is as good as capecitabine in HER-2 negative disease, strengthening the ABC Guidelines for first-line chemotherapy in patients with locally recurrent/metastatic breast cancer. Selection of a specific bevacizumab-containing regimen should be based on each patient's individual treatment priorities.

## CENTRAL NERVOUS SYSTEM MALIGNANCIES

### Dacomitinib monotherapy shows activity in patients with recurrent glioblastoma and EGFR amplification with and without EGFRvIII mutation: GEINO-11

Juan Manuel Sepúlveda, 12 de Octubre University Hospital, Madrid, Spain, presenting findings on behalf of the Spanish Group for Research in Neurooncology (GEINO) from a multicentre, 2-stage, open-label, phase II trial evaluating the efficacy and safety of dacomitinib in adult patients with recurrent glioblastoma. The study enrolled patients with tumours having EGFR gene amplification, with or without EGFRvIII mutation, since EGFR amplification is reported in approximately 50% of glioblastoma cases; furthermore, about 50% cases with amplification are associated with deletion of the extracellular ligand-binding domain, the constitutively active mutant protein EGFRvIII. Dacomitinib is a second-generation, oral, irreversible, pan-HER tyrosine kinase inhibitor (TKI), that has shown activity to EGFRvIII, and also in preclinical models of lung cancer that were resistant to erlotinib and gefitinib. Dacomitinib has been recently reported to inhibit tumour growth in glioblastoma cell lines having EGFR amplification.

Patients were enrolled following first disease recurrence and stratified into cohort A comprising 30 patients with EGFR gene amplification, but no EGFRvIII mutations, or cohort B comprising 19 patients with EGFR amplification plus the EGFRvIII mutation. All patients received dacomitinib at 45mg daily until disease progression, unacceptable toxicity or study end. The primary endpoint was progression-free survival (PFS) at six months (PFS-6m) according to RANO criteria. Response was MRI assessed by investigators and confirmed by an independent radiologist.

A planned interim analysis revealed that an insufficient number of cohort B patients remained progression-free at 6 months; therefore, cohort B recruitment was terminated. Overall, 6-month PFS was 11% and 13% in cohort A versus 6.3% months in cohort B. No significant difference in PFS was observed between cohorts: Overall median PFS was 2.3 months; median PFS was 2.3 months in cohort A and 1.8 months in cohort B. At 12 months, 4 patients were progression-free and 2 patients remained progression-free at 24 months. Median overall survival (OS) was 7.3 months; median OS was 7.8 months in cohort A versus 6 months in cohort B. In cohort A, one (2%) complete and one (2%) partial response were observed. The patient achieving complete response is still on treatment and shows no radiological evidence of disease after 24 months. The partial

response reported in one patient was of 12-month duration. Stable disease was achieved by 13 (26.6%) patients, 9 patients in cohort A and 4 patients in cohort B.

Diarrhea and rash were the most common adverse events (AEs); 19 (38.7%) patients experienced grade 3/4 drug-related AEs. The authors concluded that dacomitinib had limited single-agent activity in patients with recurrent glioblastoma with EGFR amplification, with or without EGFRvIII mutation but, since ongoing responses were achieved by a number of patients, biomarker assessment could be used to identify selected patients that are likely to benefit from dacomitinib. NCT01520870. Sepúlveda et al. Abstract 2902.

### Practice point and future research opportunities

Recurrent glioblastoma has a very poor prognosis with an unmet need for new treatment options and EGFR is an attractive therapeutic target. EGFR is amplified at high rates in glioblastoma and the activation of EGFR and tumour proliferation, survival, angiogenesis, and invasion have been linked. Single-agent dacomitinib has shown activity in this setting, albeit limited, but may show greater clinical benefit in biomarker-selected patients or in combination.

### EGFR amplification detected by FISH shows strongest association to radiographic response following ABT-414 treatment in patients with glioblastoma

Martin J. Van den Bent, Erasmus University Medical Centre, Rotterdam, The Netherlands presented findings from an analysis of biomarkers in glioblastoma. Noting that glioblastoma involves aberrant EGFR signalling, the investigators analysed patient samples to characterise the EGFR status. Patients with glioblastoma were treated with 3 different regimens of ABT-414, an EGFR-targeted antibody conjugated to the toxic antimicrotubule agent monomethylauristatin F, in an open-label, 3-arm, phase I study.

To determine biomarkers for ABT-414-based therapy, they measured EGFR and EGFRvIII expression using reverse transcription-polymerase chain reaction (RT-PCR), EGFR gene amplification was detected with fluorescence in situ hybridisation (FISH), and the total EGFR protein expression was analysed by immunohistochemistry (IHC). Tumour tissue from 89 patients was used to determine which marker most strongly associated with patient outcomes. IHC and RT-PCR confirmed expression of EGFR mRNA and protein was found to be correlated in glioblastoma tissue samples; the Spearman correlation was  $-0.86$  ( $p = 0.0026$ ). A strong association between

EGFR gene amplification and mRNA overexpression was observed and EGFRvIII mRNA was detected almost exclusively in cases with EGFR amplification.

EGFR amplification detected by FISH seems to be the strongest marker for patient outcome.

EGFR amplification has been confirmed in 23 of 29 glioblastoma patient samples tested.

Furthermore, EGFR gene amplification was detected in all 6 of 6 patients showing a confirmed objective radiographic response according to the Response Assessment in Neuro-Oncology criteria compared with 5 of 6 patient samples showing total EGFR mRNA overexpression and with EGFRvIII expression, which was detected in 4 of 6 patients. NCT01800695. Van Den Bent *et al.* Abstract 2903.

### Practice point and future research opportunities

This analysis used several assays to characterise the EGFR status of glioblastoma samples from patients treated with ABT-414 in an ongoing phase I trial and found that EGFR amplification detected by FISH most strongly associated with objective radiographic responses, followed by EGFR mRNA overexpression, and by EGFRvIII expression. The assays developed may be useful in patient selection to identify those most likely to respond to ABT-414.

### Analysis finds no survival advantage from valproic acid in newly patients with diagnosed glioblastoma

Valproic acid is an anti-epilepsy drug that is known to be an inhibitor of multiple enzymes and is often used as needed to control the epileptic seizures that are often seen in patients with newly diagnosed glioblastoma. Recent reports have suggested improved outcome when valproic acid was added to temozolomide, leading Michael Weller, University Hospital, Zurich, Switzerland and colleagues to conduct a combined analysis of survival between the use of anti-epileptic drugs from the inception of temozolomide chemotherapy and radiotherapy. The database included a pooled patient cohort of 1869 patients participating in one of 4 recent randomised clinical trials in newly diagnosed glioblastoma: AVAGlio (NCT00943826), RTOG-0825 (NCT00884741), CENTRIC (NCT00689221) and CORE (NCT00813943). The analysis compared progression-free (PFS) and overall survival (OS) between cohorts receiving chemoradiotherapy plus sole valproic acid, or with valproic acid plus another enzyme-inducing anti-epileptic drug or versus a non-enzyme inducing anti-epileptic drug and with no anti-epileptic drug. The investigators used Cox regression models

stratified by trial and adjusted baseline prognostic factors, including O<sup>6</sup>-methylguanine DNA methyltransferase (MGMT) promoter methylation status.

No significant improvement in PFS or OS was observed in any of the compared treatment groups over chemoradiotherapy; the comparison between valproic acid included at the beginning of chemoradiotherapy with patients receiving no anti-epileptic drug regarding PFS was HR 0.92 ( $p = 0.41$ ) and OS was HR 1.00 ( $p = 0.95$ ). The comparison in PFS between added valproic acid and an enzyme inducing anti-epilepsy drug was HR 0.95 ( $p = 0.62$ ) and OS was HR 1.02 ( $p = 0.93$ ). Finally, PFS for valproic acid compared with a non-enzyme inducing anti-epilepsy drug was HR 1.02 ( $p = 0.92$ ) and OS was HR 1.06 ( $p = 0.67$ ). The analyses were also done for levetiracetam and showed similar findings. Weller *et al.* Abstract 26LBA.

### Practice point and future research opportunities

This pooled analysis did not confirm the previous report of an association between valproic acid or levetiracetam with improved overall or progression-free survival, thus challenging the need for a phase III trial evaluating an anti-epilepsy drug add-on to the standard of care in newly diagnosed glioblastoma.

## EARLY DRUG DEVELOPMENT

### The investigational oral pan-RAF kinase inhibitor, MLN2480, is safe and shows anti-tumour activity in patients with advanced solid tumours or melanoma

Drew Warren Rasco, South Texas Accelerated Research Therapeutics, San Antonio, USA, reported results from the first-in-human phase I study evaluating the safety of MLN2480, an investigational pan-RAF kinase inhibitor. Other primary objectives included determining the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), pharmacokinetics (PK) and preliminary efficacy. MLN2480 targets RAF kinases, which play a key role in MAPK signalling that is often hyperactivated due to the MAPK pathway mutations commonly found in solid tumours. This study initially showed that 200 mg MLN2480 every other day (Q2D) had an acceptable safety profile and preliminary antitumour activity [Middleton et al, ENA 2014, Abstract 364]. However, weekly (QW) dosing is also being evaluated with the aim of achieving higher MLN2480 exposures and enhanced pathway inhibition.

The melanoma arm of this study enrolled patients with inoperable stage III/IV melanoma and the PK arm enrolled patients with advanced solid tumours; all patients were 18 or more years of age. Tumour biopsies were taken at screening and post-dose on days 21 or 22 of cycle 1. At the time of analysis, 52 patients in the melanoma and 20 patients in the PK arms received MLN2480 at 200 mg Q2D and 13 patients received 400 to 800 mg QW. In the QW dose escalation arm, 2 patients had grade 3 dose limiting toxicities (DLTs) during cycle 1 consisting of elevated bilirubin and maculopapular rash at the 800 mg dose; therefore, the MTD was set as 600 mg QW. In the Q2D and DX/QW dose escalation arms, 38% and 23% of patients, respectively, had grade  $\geq 3$  drug-related adverse events (AEs), including maculopapular rash (7%) and anaemia (8%). In all, 19% and 15% of patients in the Q2D and DX/QW arms discontinued due to AEs. The PK analysis showed that MLN2480 was rapidly absorbed with a median  $T_{max}$  of approximately 3 hours, and dose-proportional exposure with 400 to 800 mg QW dosing, with no apparent plasma accumulation after repeated QW dosing.  $C_{max}$  after day one QW dosing was similar to that at steady state for Q2D dosing over 1 cycle (equivalent doses). PD analyses are ongoing.

Decreased pERK and increased BIM expression was observed post-dose in patients in the Q2D BRAF-/NRAS-mutated melanoma arm. In the cohort of patients with melanoma and BRAF-

mutation receiving MLN2480 Q2D, 6 patients achieved partial responses (PR) lasting from 1.9 to 16.4 months, and one patient achieved stable disease (SD) lasting more than 5 months. In the cohort of Q2D patients with melanoma and NRAS mutation, one patient achieved a PR lasting 1.5 months and 3 patients experienced SD lasting from 3.5 to 5.4 months. One QW patient with BRAF mutated thyroid cancer showed PR for less than one month after receiving an 800 mg dose that was reduced to 600 mg and one 400-mg QW patient with BRAF-mutated thyroid cancer showed SD lasting 9.2 months. The investigators have decided to further evaluate the weekly dosing schedule. NCT01425008. Rasco *et al.* Abstract 300.

### Practice point and future research opportunities

MLN2480 showed acceptable safety and pharmacokinetic profiles at a dosing regimen of 400 to 600 mg administered weekly. PD results were consistent with the proposed mechanism of action of MLN2480. Preliminary antitumour activity was observed and the overall data support ongoing further investigation.

## S 49076, a novel MET/AXL/FGFR inhibitor, demonstrates anti-tumour activity in a first-in-human phase I dose-escalation study in patients with advanced solid tumours

Analia Azaro, Vall d'Hebron University Hospital, Barcelona, Spain presented findings on behalf of an international team from the first-in-human phase I dose-escalation study of S 49076, a novel MET/AXL/FGFR inhibitor. S 49076 is an ATP-competitive tyrosine kinase inhibitor (TKI) that does not inhibit VEGFR-2, but selectively targets MET, AXL and FGFR-1/2/3 kinases that are deregulated and strongly implicated in tumour progression and metastasis. S 49076 could be expected to have efficacy in treating patients with primary cancer and metastasis and also preclinical data showed a favourable pharmacological and good safety profile. This phase I open label, dose-escalation study aimed to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), pharmacokinetics (PK), pharmacodynamics (PD) and potential efficacy of an oral formulation of S 49076 in patients with advanced solid tumours. Patients received oral capsule(s) of S 49076 once (QD) or twice (BID) daily over a continuous 21-day cycle. Plasma concentrations of S 49076 were assessed to characterise the pharmacokinetics at day one and steady state and tumour evaluation was performed once every 2 cycles. The study enrolled 79 patients that were treated at doses ranging from 15 to 900 mg QD or 7.5 to 285 mg BID. The patients' characteristics were balanced across both arms; patients were 58% male, with a median age of 60 years.



At data cut-off, 69 patients had evaluable data; 38 (55%) patients who were treated at a variety of doses achieved prolonged stable disease, with a median of duration of 17.7 weeks. Maximal plasma concentration was reached between 2 and 6 hours, showed a mean oral bioavailability of approximately 30% and the elimination half-life was approximately 15 hours. Cmax and exposure increased proportionally to the dose.

Similar adverse event (AE) frequency was seen for QD and BID dosing regimens at the equivalent total daily dose. Overall, 76% of the 76 patients receiving treatment had drug-related AEs. DLTs were reported for 9 patients and the most frequent drug-related adverse events occurring in more than 15% of patients included peripheral oedema in 27.8%, hypoalbuminemia in 25.3%, yellow skin pigmentation in 20.3%, dysaesthesia in 19% and asthenia, which occurred in 17.7% of patients. The majority of these events were grades 1/2 and did not lead to S 49076 discontinuation; however, 9 patients required dose reductions.

The investigators determined that the MTD was reached at 760 mg in QD arm and 285 mg in BID arm and decided to bring the once-daily administration schedule of 600 mg S 49076 forward for further development in an expansion cohort of up to 24 patients. S 49076 in combination with other therapies will be also be evaluated. Azaro et al. Abstract 301.

### Practice point and future research opportunities

Based upon the promising anti-tumour activity demonstrated by S 49076 in a cohort of patients with advanced solid tumours, the general safety profile of oral treatment, which was good at the doses tested, and pharmacokinetic data suggesting no marked drug accumulation, further development is warranted.

## Patients with advanced solid tumours harbouring NTRK1, NTRK2, NTRK3, ROS1, and ALK gene rearrangements show objective response to entrectinib (RXDX-101)

Entrectinib (RXDX-101) shows promise for the treatment of patients with advanced solid tumours harbouring NTRK1/2/3, ROS1, or ALK molecular alterations, according to lead investigator Salvatore Siena, Niguarda Cancer Center, Ospedale Niguarda Ca' Granda, and Università degli Studi di Milano, Milan, Italy. Entrectinib is a potent oral small molecule inhibitor of the tyrosine kinases TrkA, TrkB, TrkC, which are encoded by the genes NTRK1, NTRK2, NTRK3, respectively, as well as ROS1, and ALK. Entrectinib demonstrated high potency, selectivity, and good tolerability

in two phase I studies involving patients with advanced or metastatic solid tumours having NTRK1/2/3, ROS1, or ALK molecular alterations. These studies employed a 3+3 dose escalation schema to assess safety, pharmacokinetics (PK) and the recommended phase 2 dose (RP2D). Doses ranging from 100 to 1600 mg/m<sup>2</sup> were given under both fasted and fed conditions either intermittently or in a continuous once-daily dosing (QD) regimen to 67 patients at 9 sites in the US and Italy. Plasma PK was assessed following a single dose and at steadystate, and anti-tumour activity was assessed by RECIST v1.1. The study enrolled patients with advanced or metastatic solid tumours and patients also having controlled asymptomatic central nervous system (CNS) disease at baseline were allowed. Exposures of entrectinib administered QD increased in a dose proportional manner and plasma half-life was estimated at 20 to 24 hours. The RP2D was determined as 600 mg QD, based upon 2 dose limiting toxicities (DLTs) that were observed at a fixed dose of 800 mg, approximately 500 mg/m<sup>2</sup> QD, which were grade 3 cognitive impairment and grade 3 fatigue. Both resolved upon dose interruption.

Clinical benefit was observed across a variety of tumour types, with 10 out of 11 (91%) patients who had not received prior ALK-or ROS1-inhibitors showing an objective response. Of these, one patient had previously shown intolerance to an ALK-inhibitor. These responses included 3 (100%) patients with tumours having a confirmed gene rearrangement in NTRK1/2/3, 2 (100%) patients with ALK and 5 of 6 (83%) patients harbouring confirmed ROS1. One patient having rearranged ROS1 achieved complete response. Responses were observed in non-small cell lung cancer (NSCLC), colorectal, and salivary gland cancers as early as cycle 1 and lasted more than 16 months, with 5 patients showing duration of response greater than six months. Of particular interest is a 46-year old male patient with NTRK1-SQSTM1-rearranged NSCLC who had received 4 prior lines of chemotherapy that achieved a partial response (PR) in both CNS and lung lesions, and a 22-year old female patient with a known activating ALK-mutated (F1245V) neuroblastoma who had received 4 prior lines of chemotherapy and who achieved a PR that lasted 8 months.

The most commonly reported adverse events (AEs) occurring in >15% of patients were fatigue/asthenia, and paresthesia which each occurred in 33% of patients, nausea in 30%, dysgeusia in 25%, myalgia in 19%, and vomiting which was reported for 18% of patients. Three other grade 3 AEs of asthenia, muscular weakness, and neutropenia occurred that resolved with dose interruption and/or reduction. A global basket study across multiple tumour types is enrolling patients as of January, 2016. Siena et al. Abstract 29LBA.

### **Practice point and future research opportunities**

Continued clinical development of entrectinib is supported by the tolerability and early evidence of anti-tumour activity, also in the CNS, in patients with relevant molecular alterations. Entrectinib was granted orphan drug designation in December 2015 by the EMA for the treatment of neuroblastoma.

## PF-06650808, an anti-Notch3 antibody drug conjugate shows promise in adult patients with advanced solid tumours

Lead investigator Lee S. Rosen, Cancer Institute Medical Group, Los Angeles, USA, reported results from phase I, dose escalation clinical trial done to assess the safety and tolerability of PF-06650808 and to establish the maximum tolerated dose (MTD), pharmacokinetics (PK), immunogenicity, and assess preliminary evidence of anti-tumour activity. PF-06650808 is an antibody drug conjugate (ADC) comprised of a humanised IgG1 antibody linked to a novel auristatin-based cytotoxic payload with a cleavable cysteine-reactive linker that targets Notch3. The Notch pathway plays an important role in the growth of several solid tumours, including breast and ovarian cancer and in melanoma. Specifically, Notch3 alterations, including gene amplification and upregulation are associated with poor patient survival.

Cohorts of 2 to 4 patients with treatment refractory solid tumours unselected for Notch3 expression are receiving escalating doses of PF-06650808 administered intravenously once every 3 weeks. The starting dose was 0.2mg/kg and a modified continual reassessment method with a dose limiting toxicity (DLT) rate of 25% is being utilized. PK profiling was performed using validated assays for determining ADC, unconjugated payload, and total antibody concentrations in serum at various time points during cycles 1 and 4. The mean age was 56.8 (range: 22 to 75) years in the 22 female and 5 male patients enrolled.

At the ECC, findings were reported from an analysis of 27 PF-06650808 treated patients. Two patients each received doses of 0.2, 0.4, 0.8, and 1.6mg/kg, while 5 patients received 2.4 mg, 6 patients each received 3.0 and 3.6 mg, and an additional 2 patients received 4.68 mg/kg. As of June 15, 2015, 89 cycles had been administered and DLTs were observed in 4 patients during the first cycle. The most common adverse events (AEs) of any grade (AE) included decreased appetite occurring in 56% of patients, nausea in 41%, fatigue in 37%, alopecia and dehydration, which each occurred in 30% of patients. Two patients receiving the highest dose (4.68mg/kg) experienced grade 4 neutropenia and one patient receiving 3.0mg/kg experienced grade 4 febrile neutropenia. Grade 3 AEs observed in 3 or more patients were abdominal pain, decreased lymphocyte count,

hypophosphataemia, each occurring in 3 patients, and hyponatraemia, which was seen in 4 patients.

Putative clinical activity was seen in one patient with ER-positive breast cancer who achieved a confirmed partial response (PR) and an unconfirmed PR was reported in a patient with triple negative breast cancer. Following determination of the MTD, expansion cohorts for patients with advanced breast tumours selected for high levels of Notch3 expression are planned. Rosen *et al.* Abstract LBA30.

### Practice point and future research opportunities

PF-06650808 is a novel anti-Notch3 ADC that has demonstrated a manageable adverse event profile in patients with advanced malignancies. Research using Notch3 targeting is an innovative approach to treating solid malignancies and preliminary findings showed responses in two patients with breast cancer. Targeting Notch3 may become a future treatment approach in patients with selected solid tumours.

## GASTROINTESTINAL CANCERS

### TOPGEAR shows perioperative epirubicin, cisplatin, 5-FU (ECF) chemotherapy plus preoperative chemoradiation has comparable safety to sole ECF in patients with resectable gastric cancer

Trevor Leong, Peter MacCallum Cancer Centre, Victoria, Australia discussed phase II results from TOPGEAR, a randomised phase II/III trial comparing adding pre-operative chemoradiotherapy to standard peri-operative chemotherapy of epirubicin, cisplatin, 5-FU (ECF) with perioperative ECF alone for patients with resectable gastric cancer. The phase II part of the trial recruited 120 patients from 51 sites in Australia, New Zealand, Europe and Canada to assess feasibility, safety and preliminary efficacy of preoperative chemoradiotherapy (CRT); a phase III component is planned that will recruit an additional 632 patients with resectable adenocarcinoma of the stomach or gastro-esophageal junction. Patients were randomised to receive 3 pre-and 3 post-operative cycles of ECF (chemotherapy arm), or to CRT (45 Gy with concurrent 5-FU) plus 2 cycles of ECF prior to surgery and 3 further cycles of ECF following gastric resection (chemoradiotherapy arm).

Preliminary safety results from the 120 patients randomised from September, 2009 until June 2014 showed no significant differences between the 2 treatment groups. The proportion of patients receiving preoperative chemotherapy was 93.3% in the chemotherapy group and 98.3% in the chemoradiotherapy group, while 92% of patients received preoperative chemoradiotherapy; 90% of patients in the chemotherapy group compared to 85% in the chemoradiotherapy group proceeded to surgery. Of patients undergoing surgery, 64% and 50% received postoperative chemotherapy in the chemotherapy and chemoradiotherapy groups, respectively.

The rates of grade  $\geq 3$  adverse events (AEs) in the chemotherapy group included vomiting in 6.7% of patients, diarrhoea in 11.7%, neutropenia in 40%, and febrile neutropenia in 8.3% of patients compared with 8.3%, 16.7%, 45% and 10%, respectively, in the chemoradiotherapy group. Grade  $\geq 3$  anastomotic leak occurred in 3 (5.6%) and intra-abdominal sepsis following surgery in 4 (7.4%) patients in the chemotherapy group versus 4 (7.8%) and 3 (5.9%) patients, respectively, in the chemoradiotherapy group. The investigators have proceeded to part 2 (phase III) of the trial wherein 170 patients have been recruited by the time of presentation from 55 sites. The overall survival will be the primary end point. Leong et al. Abstract 2200.

#### Practice point and future research opportunities

The Intergroup 0116 and MRC MAGIC trials, respectively, established postoperative chemoradiation and perioperative chemotherapy with epirubicin, cisplatin, 5-FU as standards of care for adjuvant therapy in resectable gastric cancer in Western countries. Phase II of TOPGEAR demonstrated that adding preoperative chemoradiotherapy to this regimen is safe and feasible; phase III efficacy findings are awaited.

## No benefit increase from adding bevacizumab to peri-operative chemotherapy in patients with resectable gastro-oesophageal adenocarcinoma

David Cunningham, Royal Marsden NHS Trust, London, UK presented findings from the UK Medical Research Council, multicentre, open-label, phase II/III randomised ST03 trial, which assessed the safety and efficacy of adding bevacizumab to standard chemotherapy in patients with histologically proven, resectable, gastric/gastro-oesophageal junction or lower oesophageal adenocarcinoma. From 2007 to 2014, 1063 patients were recruited from 87 UK centres and randomised 1:1 to receive either the standard treatment comprising 3 pre- and 3 post-operative cycles of epirubicin at 50 mg/m<sup>2</sup> i.v., cisplatin 60 mg/m<sup>2</sup> i.v., and capecitabine at 1250 mg/m<sup>2</sup> (ECX) and surgery, or to the investigational arm, wherein bevacizumab at 7.5 mg/kg on day 1 was added to ECX/surgery and followed by 6 maintenance cycles of bevacizumab (ECX/B) every 3 weeks. Surgical techniques were pre-specified and laparoscopic procedures were allowed after quality assurance review. The primary outcome measure was overall survival (OS) and secondary outcomes included disease-free survival (DFS), progression-free survival (PFS), chemotherapy response rate and curative resection rate.

After a median follow-up of 33 months, 233 ECX and 239 ECX/B patients had died. No significant difference in OS between the treatments was observed, HR 1.067 (p = 0.478). The 3-year survival rates were 48.9% with ECX versus 47.6% with ECX/B. Similar rates in the treatment groups were also seen for DFS, HR 1.006 (p = 0.943) and for PFS, HR 1.026; (p = 0.768). Response rates to pre-operative chemotherapy were also similar between the groups; response rates overall were 32% with ECX versus 30% with ECX/B, and 39% versus 38% in the respective groups in patients undergoing surgery. No significant difference was observed between the groups regarding curative resection rates, which were 59% with ECX versus 55% with ECX/B in all patients, and 66% with ECX versus 64% with ECX/B in patients undergoing surgery.



Similar toxicity during chemotherapy was observed in both groups. Accrual of patients requiring oesophago-gastrectomy was closed early for the ECX/B group after an elevated post-operative anastomotic leak rate was seen in this group in patients following oesophago-gastrectomy; 9% of ECX versus 23% of ECX/B patients underwent oesophago-gastrectomy. The rates of any post-operative complication were 48% with ECX versus 56% with ECX/B. Rates of post-surgical life-threatening complications were 7% and 8% in the ECX and ECX/B groups, respectively. NCT00450203. Cunningham *et al.* Abstract 2201.

### Practice point and future research opportunities

The standard of care for resectable gastro-oesophageal adenocarcinoma is peri-operative epirubicin, cisplatin, and capecitabine plus surgery. Although bevacizumab plus chemotherapy improved response rates and progression-free survival but not overall survival in advanced gastric cancer (Ohtsu JCO 2011), this trial does not support adding bevacizumab to the standard of care in resectable gastro-oesophageal adenocarcinoma.

### ICECREAM trial identifies subgroup of patients with metastatic colorectal cancer and rare KRAS mutation that responds to therapy with an EGFR agent plus irinotecan

Patients with metastatic colorectal cancer (mCRC) and KRAS exon 2 c.38G>A: pGly13Asp (G13D mutation) receiving cetuximab together with irinotecan demonstrated both objective responses and some delay of disease progression, according to results from the phase II ICECREAM trial presented by Eva Segelov, University of New South Wales, Sydney, Australia. She reported results on behalf of the Australian Gastrointestinal Trials Group (AGITG) that also confirmed the lack of activity of cetuximab monotherapy in patients with G13D mutated mCRC, which has previously been reported in smaller series.

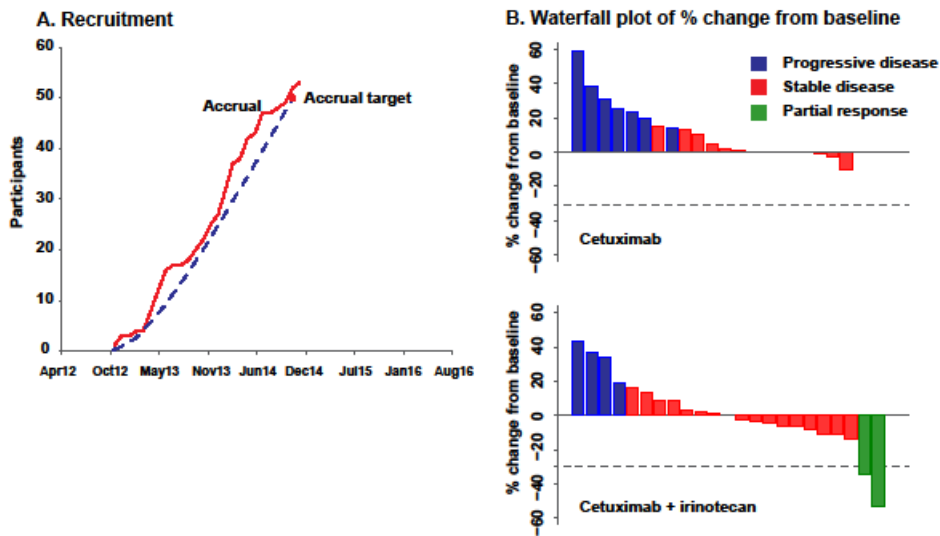
The importance of these findings is underscored by the fact that patients with mCRC and KRAS or NRAS mutations are generally not offered EGFR inhibitors due to lack of response to these agents. However, there is a 40% incidence of KRAS mutations in CRC, with approximately 19% of these mutations consisting of KRAS G13D mutation; the absolute incidence of the G13D mutation is 8% in mCRC and represents a subgroup of patients likely to respond to EGFR therapy. Additionally, several retrospective clinical reports suggested treatment benefit with cetuximab in patients with mCRC and G13D mutation that may be similar to that seen in patients with KRAS



wild-type tumours. However, these reports have been confounded by small sample sizes and by co-administered chemotherapy, making it difficult to isolate the actual effect of the EGFR inhibitors. Furthermore, adding irinotecan to agents targeting EGFR has been shown to increase the response rate and to delay progression in patients with KRAS unselected mCRC, leading investigators to anticipate that irinotecan could potentiate the response in patients with G13D mutated tumours.

ICECREAM enrolled patients with mCRC, ECOG PS 0-2 that were refractory to irinotecan, which was defined as having progressed within 6 months of irinotecan treatment and being intolerant of or refractory to fluoropyrimidine and oxaliplatin, to directly compare the efficacy of cetuximab versus combined cetuximab/irinotecan. Patients were stratified by G13D mutation or by wild-type KRAS, NRAS, BRAF and PI3KCA genes (this arm still accruing) and randomised 1:1 to receive either cetuximab at 400 mg/m<sup>2</sup> i.v. loading then 250 mg/m<sup>2</sup> weekly or the same cetuximab regimen plus irinotecan at 180 mg/m<sup>2</sup> every two weeks. Patient characteristics were well balanced between treatment groups, except age (61 versus 66 years), time since first metastatic diagnosis (19.1 versus 28.1 months), and time since last irinotecan dose (2.8 versus 4.8 months) in the cetuximab and cetuximab/irinotecan arms, respectively.

Results for the G13D cohort of 51 patients were reported at the ECC showing a 6-month progression-free survival (PFS) rate of 10% (95% CI 2%, 26%) in the cetuximab arm compared to 23% (95% CI 9%, 40%) in the cetuximab/irinotecan arm, HR 0.75 (95% CI 0.42, 1.33). The median time to progression was similar in the respective arms at 2.5 versus 2.6 months. Complete response (CR) was not demonstrated in either treatment arm and no partial response (PR) was seen in the cetuximab monotherapy arm; however, 9% of patients receiving combination therapy achieved a PR. Stable disease was achieved by 58% of patients receiving cetuximab compared with 70% of patients in the cetuximab/irinotecan arm.



**Caption:** AGITG ICECREAM study.

Panel A: Recruitment to the study exceeded projection despite this being a rare molecular subtype of colorectal cancer.

Panel B: Best response for target lesions by patient for the Cetuximab arm (above) and Cetuximab plus Irinotecan arm (below), based on maximum tumour reduction with no new lesions, coloured by RECIST best response.

**Credit:** Eva Segelov

Consistent with previous studies, one or more grade 3/4 event occurred in 11 (44%) patients receiving monotherapy and in 16 (64%) patients receiving combination therapy. Segelov et al. Abstract 32LBA.

### Practice point and future research opportunities

ICECREAM is the first trial to date providing prospective data on treatment in patients with a rare molecular subtype of colorectal cancer, KRAS G13D mutation. These findings contribute to the management of these patients. While no evidence for treating G13D mutant colorectal cancer with cetuximab or panitumumab monotherapy is provided, the results may support using combined cetuximab/irinotecan in this cohort. Combination therapy, but not cetuximab monotherapy, may

warrant further evaluation to confirm whether irinotecan acts synergistically with EGFR inhibitors in patients with mCRC and G13D mutation. Data from the cohort of KRAS wild-type patients participating in the ICECREAM study is eagerly awaited, which may identify markers beyond RAS for determination of resistance to anti-EGFR antibodies.

## Improved outcome in subgroup of patients with stage II rectal cancer and high-risk disease receiving adjuvant chemotherapy following pre-operative short course radiotherapy

After noting that adjuvant chemotherapy is most often offered to renal cancer patients with high-risk disease who received a long course of chemoradiotherapy, Jonathan Loree, British Columbia Cancer Centre, British Columbia, Canada presented findings from a study that evaluated the benefit in patients with pathologic stage II rectal cancer receiving adjuvant chemotherapy following pre-operative short course radiotherapy (SCRT).

The retrospective study analysed data from the 5 regional cancer centres in British Columbia between 1998 and 2009 of patients diagnosed with stage II (pT3/4 pN0) tumours following SCRT, focusing on the 123 (37.3%) patients who also received adjuvant chemotherapy. Patients receiving adjuvant chemotherapy were younger, with a median age of 61 years compared with 73 years in the overall cohort of patients experiencing recurrence following SCRT who did not receive adjuvant chemotherapy ( $p < 0.0001$ ). Patients receiving adjuvant chemotherapy also had a better ECOG PS ( $p < 0.001$ ), and more high-risk features ( $p < 0.0001$ ) than patients not receiving adjuvant chemotherapy. Median follow-up was 8.57 years in the adjuvant chemotherapy arm and 7.92 years in the non-adjuvant chemotherapy arm.

Univariate analysis showed a significant association between adjuvant chemotherapy and improved overall survival (OS), HR 0.42; 95%CI 0.30, 0.59 ( $p < 0.0001$ ); adjuvant chemotherapy was also associated with prolonged disease specific survival (DSS), HR 0.58; 95%CI 0.36, 0.94 ( $p = 0.028$ ), and recurrence-free survival (RFS), HR 0.62; 95%CI 0.39, 0.98 ( $p = 0.043$ ). These associations did not remain significant in multivariate analysis; the association between adjuvant chemotherapy and OS was HR 0.62, 95%CI 0.37, 1.03 ( $p = 0.064$ ); DSS HR 0.83; 95%CI 0.43, 1.61 ( $p = 0.58$ ), and the association between adjuvant chemotherapy and RFS was HR 0.82; 95%CI 0.44, 1.50 ( $p = 0.51$ ). Further analysis revealed that only the subgroups of patients with  $\geq 2$  high-risk features showed benefit following adjuvant chemotherapy: OS, HR 0.22; 95%CI 0.069, 0.70, ( $p$

= 0.011), DSS, HR 0.25; 95%CI 0.07, 0.89, ( $p = 0.033$ ), and RFS was HR 0.24; 95% CI 0.07, 0.85 ( $P = 0.027$ ). Loree *et al.* Abstract 2002.

### Practice point and future research opportunities

In this study, univariate analysis showed an association with improved overall survival in patients receiving adjuvant chemotherapy following pre-operative short course radiotherapy in stage II rectal cancer that was not confirmed by multivariate analysis. In this population-based cohort of patients with stage II rectal cancer, adjuvant chemotherapy after short course radiotherapy did not improve outcomes in unselected patients, however the presence of two or more clinicopathological risk factors may identify patients who benefit from adjuvant chemotherapy following short course radiotherapy.

### Patient age and disease category may influence outcomes for patients with stage II-III resectable rectal cancer receiving preoperative chemoradiotherapy or radiotherapy prior to surgery

Laura Kairevice, Lithuanian University of Health Sciences Academy of Medicine, Kaunas, Lithuania presented findings on behalf of colleagues from a randomised controlled trial that sought to determine which neoadjuvant treatment is superior in the stage II-III resectable rectal cancer setting. The investigators conducted a head to head comparison of treatment with standard chemoradiotherapy (CRT; preoperative conventional CRT, 50 Gy/25 fr, 2Gy/fr with 5-FU 400mg/m<sup>2</sup>/d i/v 1–4d and LV 20mg/m<sup>2</sup>/d i/v 1–4d on the 1<sup>st</sup> and the 5<sup>th</sup> week of radiotherapy (RT) followed by surgery after 6 to 8 weeks and then by 4 adjuvant cycles of 5-FU 425mg/m<sup>2</sup>/d i/v and LV 20mg/m<sup>2</sup>/d i/v 1–5d every 4 weeks) versus RT (preoperative short-term RT, 25Gy/5fr, 5Gy/fr followed by surgery in 6 to 8 weeks). Data from 72 patients in the CRT arm and 68 in the RT arm were included in the statistical analysis. The baseline characteristics of age, sex, tumour localisation in the rectum, cT, cN, and clinical stage were similar in both arms ( $p > 0.05$ ).

The analysis was done after a median follow-up of 43 (range: 6 to 80) months and revealed disease-free survival (DFS) and overall survival (OS) were superior with CRT over RT; the 5-year DFS rate was 69% with CRT versus 44% with RT ( $p = 0.011$ ) and 5-year OS was 76% with CRT versus 64% with RT ( $p = 0.055$ ).

By univariate analysis, the risk for disease progression was 1.9-fold higher after RT versus CRT ( $p = 0.0187$ ), and 2-fold higher for patients aged 65 years or more ( $p = 0.0107$ ); it was also

determined that risk of progression increased by 2.2-fold for cN2 ( $p = 0.039$ ), and by 2.9-fold higher for ypN2 ( $p = 0.0056$ ), as compared to cN0 and ypN0 category patients, respectively. The risk for death was 3.7-fold higher for patients aged 65 years or more ( $p = 0.0009$ ), 2.5-fold higher for cN2 patients ( $p = 0.042$ ) and 3-fold higher for ypN2 patients ( $p = 0.023$ ). CRT showed an influence on reducing the risk for death of 1.8-fold, as compared to RT that did not reach statistical significance ( $p = 0.0585$ ). NCT0059731. Klarevice *et al.* Abstract 2004.

### Practice point and future research opportunities

Findings from this study favour adjuvant chemoradiotherapy over radiotherapy alone and identified older patients and disease categories cN2 and ypN2 as factors that may indicate poorer disease-free survival in patients with stage II-III resectable rectal cancer undergoing adjuvant treatment plus surgery.

## GENITOURINARY MALIGNANCIES

### Significantly improved overall survival with nivolumab compared with everolimus in previously treated advanced renal cell carcinoma: Results from CheckMate 025

Padmanee Sharma, MD Anderson Cancer Center, USA presented findings during the Presidential Session from the CheckMate 025 phase III clinical trial showing that nivolumab significantly prolongs overall survival (OS) in patients with advanced kidney cancer, who progressed after their first treatment. CheckMate 025 compared nivolumab with the standard treatment, everolimus, in patients with clear cell renal cell carcinoma. This is the first trial to show improved OS in these patients for any immune checkpoint inhibitor drug; which target molecules playing a role in the immune system's ability to recognise and attack tumours; specifically, nivolumab blocks the interaction between the programmed cell death protein 1 (PD-1) and its ligand PD-L1.

Between October 2012 and March 2014, the trial enrolled 821 patients with advanced clear cell kidney cancer, or metastatic renal cell carcinoma who had received 1 to 2 prior anti-angiogenic therapies and  $\leq 3$  systemic therapies, having measurable disease (RECIST v1.1), and a Karnofsky performance status  $\geq 70\%$  that were randomised 1:1 to 3 mg/kg of i.v. nivolumab every two weeks or an oral daily 10 mg tablet of everolimus.

A preplanned interim analysis done after a minimum 15 months follow-up revealed a clear survival advantage with nivolumab over everolimus. Therefore, the trial was terminated early in July 2015 and patients receiving either drug were offered the opportunity to continue with nivolumab. Median OS was 25.0 (95%CI 21.8, NE) with nivolumab versus 19.6 months (95% CI 17.6, 23.1 months) with everolimus, HR 0.73; 95% CI 0.57, 0.93 ( $p = 0.0018$ ). Progression free-survival was median 4.6 (95% CI 3.7, 5.4) versus 4.4 (95% CI 3.7, 5.5) months with nivolumab and everolimus, respectively, HR 0.88; 95% CI 0.75, 1.03 ( $p = 0.1135$ ).

Also, tumour shrinkage was greater in response to nivolumab than to everolimus. The objective response rate (ORR) was 25% for patients receiving nivolumab versus 5% for patients on everolimus, odds ratio 6.05; 95% CI 3.69, 9.91 ( $p < 0.0001$ ). Complete response was achieved by 4 (1%) nivolumab patients versus two (1%) everolimus patients and 98 (24%) versus 20 (5%) nivolumab versus everolimus patients achieved partial response. Stable disease occurred in 139 (34%) nivolumab patients versus 227 (55%) everolimus patients.

The survival benefit with nivolumab was seen in patients regardless of the extent of PD-L1 tumour expression; median OS with nivolumab and everolimus, respectively, was 21.8 versus 18.8 months in patients with PD-L1 expression  $\geq 1\%$  compared with 27.4 versus 21.2 months in patients with expression  $< 1\%$ .

Fewer treatment related adverse events (TRAEs) of any grade occurred with nivolumab than with everolimus; TRAEs were seen in 79% of nivolumab versus 88% of everolimus patients. The most commonly reported with nivolumab were fatigue in 33%, nausea in 14%, and pruritus in 14% of patients compared with fatigue in 13%, 30% stomatitis, and 24% of patients experiencing anaemia with everolimus. Grade 3 or 4 TRAEs occurred in 19% of nivolumab and 37% of everolimus patients. No treatment-related deaths occurred in the nivolumab arm and 2 deaths occurred in the everolimus arm. These results were published simultaneously in the NEJM [N Engl J Med 2015; 373:1803-13]. NCT01668784. Sharma *et al.* Abstract 3LBA.

### Practice point and future research opportunities

CheckMate 025 is the first and only study in which an immune checkpoint inhibitor has shown a clear overall survival benefit, when used after prior treatment has failed in patients with advanced kidney cancer. Treatment options are currently limited for patients with renal cell carcinoma, which is the most common type of kidney cancer in adults. Patients with this cancer have a poor prognosis, so effective treatments are desperately needed. These results are significant and clinically meaningful and are likely to change the treatment of patients with advanced kidney cancer, whose disease has progressed on prior treatment. The finding that overall survival was higher among patients treated with nivolumab, irrespective of PD-L1 expression prior to treatment, suggests that nivolumab should be offered regardless of the patient's PD-L1 expression status.

### Cabozantinib out-performs everolimus in patients pretreated for advanced renal cell carcinoma

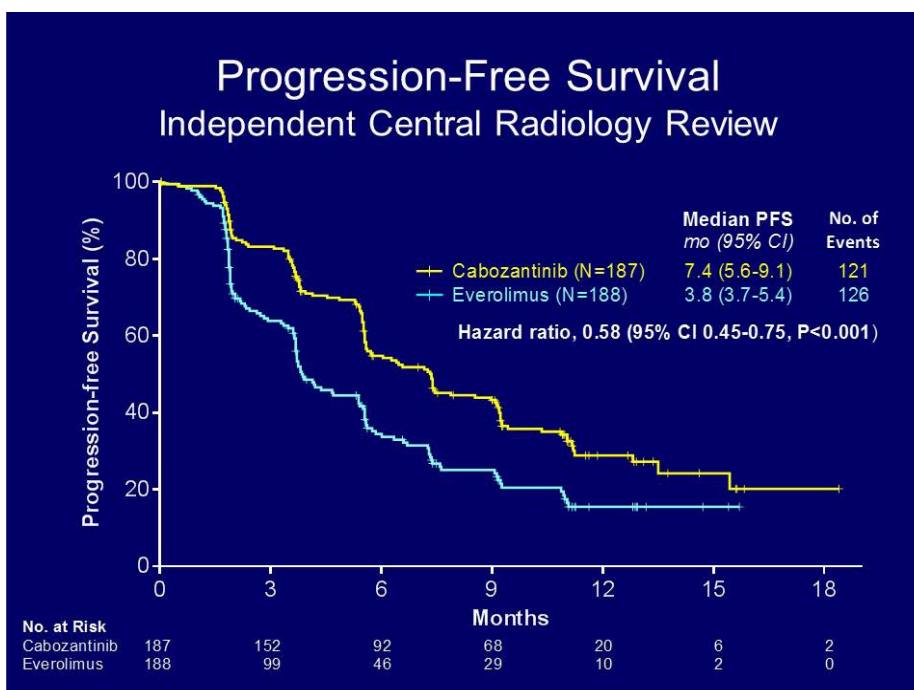
Results from prespecified subgroup analyses for progression-free survival (PFS) from the open-label phase III METEOR trial were reported by lead investigator Toni Choueiri, from the Dana Farber Cancer Institute in Boston, USA, that showed treatment with cabozantinib reduced the rate of disease progression or death by 42% compared to everolimus in patients with advanced clear-cell renal cell carcinoma (RCC). Cabozantinib inhibits multiple tyrosine kinases (TK), including MET, VEGFR, AXL and RET. Based upon results from the METEOR trial, cabozantinib was



granted Breakthrough Therapy Designation by the US FDA on 24 August 2015 for patients with RCC who experienced disease progression following treatment with a TKI; cabozantinib is currently authorised for treatment of adult patients with progressive, unresectable locally-advanced, or metastatic medullary thyroid cancer.

In METEOR, 658 patients with measurable disease by RECIST 1.1 and Karnofsky performance status  $\geq 70\%$  were stratified by MSKCC prognostic criteria and by the number of prior treatments with vascular endothelial growth factor receptor (VEGFR) TKIs, then randomised 1:1 between August 2013 and November 2014, to receive daily administration of cabozantinib at 60 mg or everolimus at 10 mg. Patients were required to have progressed within 6 months of their prior treatment with VEGFR TKIs; 71% of patients had undergone treatment with one and 29% of patients had received 2 or more prior VEGFR TKIs. According to MSKCC criteria, 46% of patients were favourable, 41% intermediate, and 13% of patients were classified as poor risk.

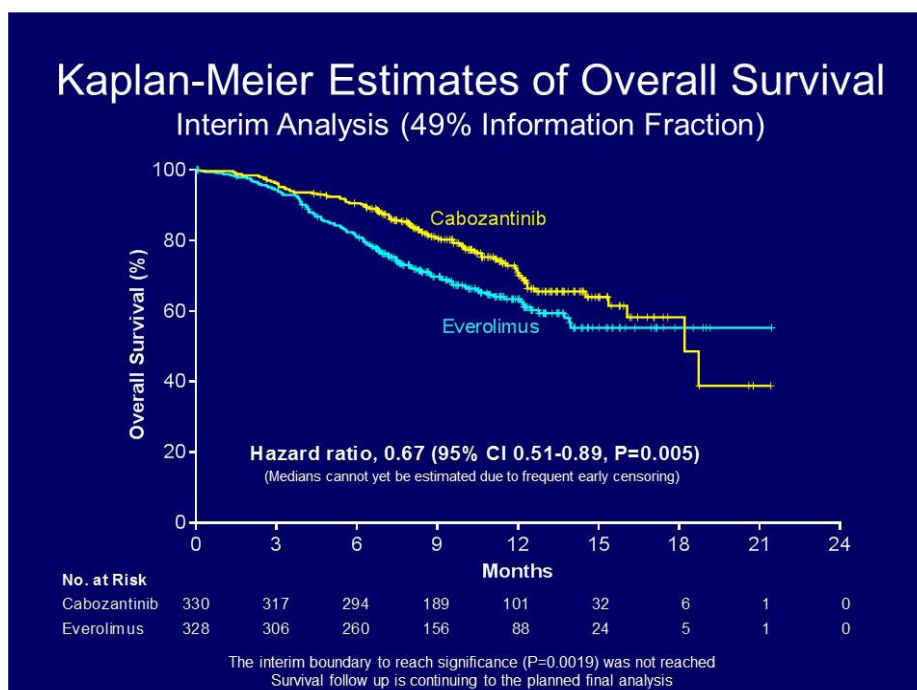
Improved PFS and overall response rate (ORR) were demonstrated with cabozantinib over everolimus in patients with advanced clear-cell RCC who had been pretreated with VEGFR TKIs. The study met the primary endpoint of PFS per independent radiology committee; the estimated median PFS among the first 375 randomised patients was 7.4 months with cabozantinib compared to 3.8 months with everolimus, HR 0.58; 95% CI 0.45, 0.75 ( $p < 0.001$ ).



**Caption:** Progression-free survival in the METEOR Phase III trial of cabozantinib vs everolimus in metastatic renal cell carcinoma.

**Credit:** Toni Choueiri, et al.

Secondary endpoints, including the ORR and overall survival (OS), also favoured cabozantinib; ORR was 21% with cabozantinib compared to 5% with everolimus ( $p < 0.001$ ). At the interim OS analysis (49% information fraction) a trend towards prolonged survival for patients receiving cabozantinib was seen although the median OS could not yet be estimated; the HR was 0.67; 95% CI 0.51, 0.89 ( $p = 0.0050$ ) for the comparison of cabozantinib with everolimus. The criteria for early rejection of the hypothesis were not met at this time point ( $p \leq 0.0019$ ).



**Caption:** Overall survival in the METEOR Phase III trial of cabozantinib vs everolimus in metastatic renal cell carcinoma.

**Credit:** Toni Choueiri, et al.

Cabozantinib was well tolerated by patients in this setting. The most commonly reported serious adverse events (SAEs) with cabozantinib were abdominal pain, pleural effusion, and diarrhoea,

which occurred in 3%, 2.7%, and 2.1% of patients, respectively. SAEs with everolimus included anaemia, dyspnoea, and pneumonia, which were each reported in 3.7% of patients. Treatment discontinuation due to adverse events was reported for 9.1% of patients receiving cabozantinib and 10% of patients receiving everolimus.

The authors suggest that these data will impact treatment decisions for patients with advanced clear-cell RCC and may change the treatment landscape altogether. The study was simultaneously published in the NEJM [N Engl J Med 2015; 373:1814-1823]. NCT01865747. Choueiri et al. Abstract 4LBA. Practice point and future research opportunities Enormous progress in the management of renal cell cancer has been recently made with 7 new drugs approved on the basis of progression-free survival. Although METEOR reached its primary endpoint, the overall survival data are not mature; cabozantinib could potentially become the standard in advanced renal cell carcinoma. Cabozantinib may also be relevant in the second or later line treatment option.

### Similar overall survival demonstrated with axitinib and sorafenib as first-line therapy in patients with metastatic renal cell carcinoma

Although approved for treatment of advanced renal cell carcinoma (RCC) in the second line, previous results from this randomised phase III trial in treatment-naïve patients demonstrated that axitinib, a selective inhibitor of VEGFR, significantly improved the objective response rate (ORR) compared with sorafenib. At the ECC, lead investigator Thomas E. Hutson, Baylor University Medical Center, Houston, USA, presented results from an analysis of overall survival (OS) from a direct comparison of axitinib with sorafenib as first-line therapy. The trial enrolled 288 treatment-naïve patients with measurable (per RECIST v1.0), clear-cell metastatic RCC and ECOG PS 0 or 1 from Eastern Europe (51%), Asia (25%), North America (14%), and South America (10%). Patients were stratified by ECOG PS and randomised 2:1; 192 patients received open-label axitinib at 5 mg twice daily and 96 patients received sorafenib at 400 mg twice daily. The primary endpoint of progression-free survival (PFS) and secondary endpoint of ORR were previously reported.

Median OS in the overall population of patients after long-term follow-up was similar with axitinib and sorafenib; median OS was 21.7 (95%CI 18.0, 31.7) months with axitinib versus 23.3 (95%CI 18.1, 33.2) with sorafenib, stratified HR 0.995; 95%CI 0.731, 1.356 (1-sided p = 0.4883). However, patients with ECOG PS 0, showed numerically improved OS with axitinib of 41.2 (95%CI 29.2, not estimable [NE]) months versus 31.9 (95%CI 18.1, NE) months with sorafenib, HR 0.811; 95%CI 0.522, 1.259 (1-sided p = 0.1748). Patients with ECOG PS 1 showed an OS advantage with

sorafenib; median OS was 14.2 (95%CI 9.4, 18.1) months with axitinib versus 19.8 months (95%CI 12.3, 25.8) with sorafenib, HR 1.203; 95%CI 0.778, 1.859 (1-sided  $p = 0.7973$ ). The incidence and severity of common adverse events were consistent with previous reports of each agent. The authors suggest that the noteworthy difference in median OS in patients with axitinib by ECOG PS (PS 0 compared with PS 1), which was 41.2 versus 14.2 months, respectively, may have been influenced by practice standards in resource-limited regions, where most patients were enrolled, and by subjectivity in classifying patients to ECOG PS categories. NCT00920816. Hutson *et al.* Abstract 2509.

### Practice point and future research opportunities

Axitinib, is approved to treat advanced RCC after 1 prior systemic therapy, but has demonstrated an improved objective response rate, as well as, progression-free and overall survival comparable to sorafenib in previously untreated patients with metastatic RCC. The authors noted the large difference between median overall survival with axitinib according to ECOG performance status and suggest possible confounding factors. Further investigation of first-line axitinib is warranted, as is, clarification of this issue.

### IMA901 multi peptide cancer vaccine added to sunitinib fails to show survival advantage over sole sunitinib as first-line therapy for patients with advanced/metastatic renal cell carcinoma

There was no improvement in overall survival (OS) from adding IMA901 to first-line sunitinib in patients with advanced renal cell cancer (RCC); OS was comparable in both arms in favourable risk patients and longer OS was observed in intermediate-risk patients with sole sunitinib. Therefore, methods to improve immune responses would need to be identified before further development of IMA901 in metastatic RCC (mRCC) is indicated, according to lead author Brian Rini, Case Western Reserve University, Cleveland, USA. He presented findings from a phase III trial designed to demonstrate the OS benefit of the cancer vaccine, IMA901, in combination with standard first-line sunitinib therapy in patients with mRCC compared to sunitinib monotherapy. IMA901 is based on naturally presented tumour-associated peptides (9 HLA-A\*02- and 1 HLA-DR-binding peptides) that has shown promise in a phase II trial. This trial enrolled 339 previously untreated HLA-A\*02-positive patients with mRCC who were randomised 3:2 to receive up to 10 intradermal vaccinations of IMA901 plus 75 µg GM-CSF and standard sunitinib versus sunitinib alone. Patients in the vaccine arm were given a single infusion of cyclophosphamide 3 days before

the first vaccination to reduce regulatory T cells. Patients were stratified according to risk group (Heng), nephrectomy, and region.

The primary analysis showed no significant difference in OS between the treatment arms; median OS for sunitinib monotherapy was not reached [NR] compared with 33.1 months with IMA901/sunitinib, HR 1.34

( $p = 0.08$ ). The OS according to stratified subgroups showed favourable-risk patients had median OS of 33.7 months versus NR with sunitinib and IMA901/sunitinib, respectively, HR 0.82 ( $p = 0.59$ ); however, longer OS was observed for sole sunitinib in intermediate-risk patients; median OS was NR versus 27.8 months, respectively, HR 1.52 ( $p < 0.05$ ). The independent central review also showed comparable outcomes among patients in both arms; PFS was 15.1 versus 15.1 months, HR 1.05 ( $p = 0.62$ ). However, PFS by investigator assessment showed a trend for longer PFS that favoured the sunitinib monotherapy; median PFS was 17.9 versus 15.1 months, respectively, HR 1.18 ( $p = 0.19$ ) possibly due to the higher sunitinib exposure occurring in the monotherapy arm of median 13.7 with sunitinib arm versus 11.2 grams with IMA901/sunitinib.

IMA901 was well-tolerated and similar rates of adverse events (AEs) observed in both arms. Transient injection-site reactions were the most frequently reported AEs with IMA901. Immune data showed that sunitinib led to a significant decrease in monocytes after the first injection. There was no clear or significant association between T-cell responses and clinical outcome. Rini *et al.* Abstract 17LBA.

### Practice point and future research opportunities

The IMA901 vaccine added to sunitinib failed to improve outcomes over sunitinib as first-line therapy for patients with advanced/metastatic RCC. Although phase II results showed a survival difference with the vaccine in patients with RCC premedicated with cyclophosphamide who developed immune responses, these data were not replicated in this phase III trial and further development of IMA901 is not supported at this time.

## STAMPEDE shows adding docetaxel to hormone therapy improves survival in patients with hormone-naïve prostate cancer

Nicholas D. James, University of Warwick, Coventry, UK presented findings on behalf of colleagues from the STAMPEDE trial, which is the largest randomised clinical trial of treatment for men with prostate cancer ever conducted. STAMPEDE is an ongoing randomised clinical trial in

men with high-risk locally advanced or metastatic prostate cancer starting long-term hormone therapy for the first time that uses a multi-arm multi-stage (MAMS) design, allowing several treatments to be assessed against a single control arm. Updated survival data were presented at the ECC from 2,962 men who were assigned to 4 cohorts: Standard of care (SOC; at least two years of hormone therapy), SOC plus docetaxel (75 mg/m<sup>2</sup> for six 3-weekly cycles with prednisolone at 10 mg daily), SOC plus zoledronic acid (4 mg for six 3-weekly cycles then 4-weekly up to 2 years), or SOC plus both docetaxel and zoledronic acid. The primary endpoint was overall survival (OS). Patients were followed up for a median of 43 months.

Patients receiving docetaxel/SOC (HR 0.78; p = 0.006) or combined docetaxel and zoledronic acid/SOC (HR 0.82; p = 0.022) showed a survival advantage compared to SOC that was not observed in patients receiving zoledronic acid/SOC (HR 0.94; p = 0.45). Docetaxel improved survival by 10 months over SOC; median survival was 77 months with docetaxel versus 67 months with SOC. Adding zoledronic acid to docetaxel did not seem to increase the benefit observed with sole docetaxel (HR 1.06; p = 0.592).

The time to first reported symptomatic skeletal event (SSE) was prolonged compared to SOC in both docetaxel arms; docetaxel (HR 0.60; p < 0.0001), and docetaxel/zoledronic acid (HR 0.55; p < 0.0001) but not with sole zoledronic acid (HR 0.88; p = 0.213). In the docetaxel, combination, and zoledronic acid arms, respectively, 112, 108, and 153 SSEs occurred. In men presenting with newly diagnosed bony metastasis, zoledronic acid did not prolong the time to first reported SSE (HR 0.94; p = 0.556). Osteonecrosis of the jaw was reported in 11 patients receiving zoledronic acid and in 19 patients receiving docetaxel plus zoledronic acid, but not in the other arms. In the docetaxel, docetaxel/zoledronic acid, and zoledronic acid groups 175, 187 and 201 deaths occurred compared to 415 deaths in the SOC only cohort. Of these, 3 deaths in the docetaxel arm and 8 deaths in the docetaxel/zoledronic acid arms were determined to be treatment-related.

James *et al.* Abstract 19LBA.

### Practice point and future research opportunities

STAMPEDE shows that survival is clinically and statistically significantly improved by adding docetaxel to long-term hormone therapy in treatment naive patients beginning treatment. Docetaxel also prolonged the time to first symptomatic skeletal event, whereas zoledronic acid, either alone or in combination, did not.



## Orteronel shows promising anti-tumour activity in metastatic castration resistant prostate cancer

Lead investigators Silke Gillesen, of the Kantonsspital St. Gallen, and Richard Cathomas, of the Kantonsspital Graubünden in Chur, Switzerland presented results showing that orteronel used as switch maintenance therapy had clinical benefit in patients with metastatic castration-resistant prostate cancer (mCRPC). Orteronel is an investigational oral, non-steroidal, selective inhibitor of 17,20-lyase, a key enzyme in the production of steroidal hormones, including androgens. This multicentre randomised double-blind placebo-controlled phase III study was designed to enroll 96 patients; however just 47 patients were enrolled between November 2012 and June, 2014; 23 patients were randomised to orteronel at 300 mg twice daily plus best supportive care (BSC) and 24 to placebo plus BSC. The median patient age was 70 years (range: 51 to 85 years) and all patients had non-progressive disease after receiving a cumulative dose of  $\geq 300$  mg/m<sup>2</sup> of first line docetaxel. Orteronel plus BSC was initiated at 3 to 6 weeks after the final administration of docetaxel. The trial's primary endpoint was median event-free survival (EFS), which was defined as the time from randomisation to death, or a combination of at least two outcomes that included radiographic, clinical or prostate specific antigen (PSA) progression. Secondary endpoints included PSA decline >50%, time to PSA progression, radiographic PFS (rPFS), toxicity, quality of life (QoL) and overall survival (OS).

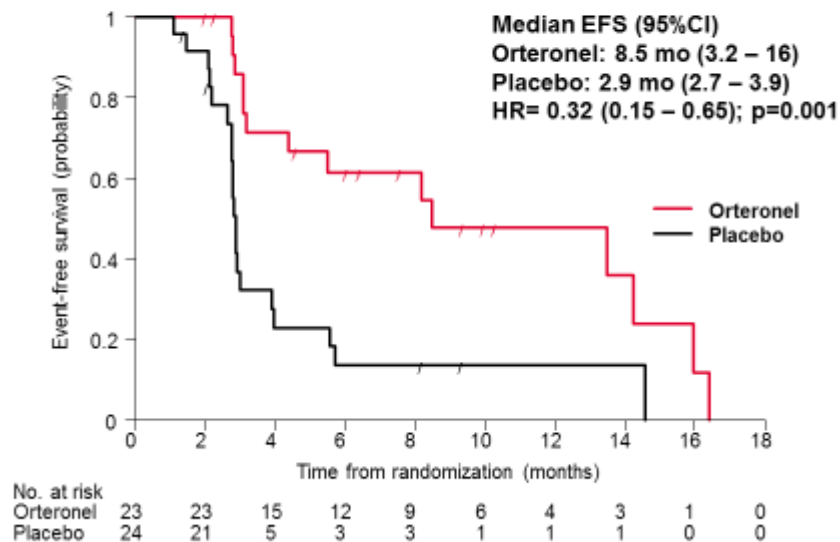
The study was halted prior to completing enrollment when Takeda Pharmaceutical announced on June 19, 2014 that it was ending the development of orteronel in prostate cancer after 2 phase III clinical trials found that orteronel plus prednisone extended time to disease progression but not OS in patients with mCRPC.

At the time of the impromptu termination, the median patient follow-up was 17 months. Patients on orteronel maintenance achieved EFS that was nearly three times longer than similar patients receiving placebo. EFS

was 8.5 (95% CI 3.2, 16.0) months with orteronel versus 2.9 (95% CI 2.7, 3.9) months with placebo, HR 0.32 (95% CI 0.15, 0.65;  $p = 0.001$ ). PSA decline >50% was observed in 57% of orteronel patients compared to just 4% of placebo patients. The time to PSA progression was also significantly increased to 6.5 months with orteronel compared to 1.8 months with placebo (HR 0.37; 95% CI 0.18, 0.75;  $p = 0.004$ ), and rPFS was 8.5 versus 2.8 months with orteronel and placebo, respectively, (HR 0.42; 95% CI 0.20, 0.91;  $p = 0.02$ ).



## Maintenance orteronel after prior disease stabilisation with docetaxel significantly prolongs event-free survival in mCRCP patients



**Caption:** Maintenance orteronel after prior disease stabilisation with docetaxel significantly prolongs event-free survival in mCRPC patients.

**Credit:** Richard Cathomas

Adverse events were reported in 61% of orteronel versus 83% of placebo patients during treatment. Higher, but manageable, toxicity occurred in the orteronel arm. Grade 2 toxicity events with orteronel included fatigue in 17%, nausea in 26%, hypertension in 17%, and hypokalaemia in 17% of patients, whereas grade 2 fatigue, nausea, and hypertension each occurred in 4% and hypokalaemia was reported in 13% of patients receiving placebo. Grade 3 fatigue, hypertension, and hypokalaemia were reported in 9%, 9%, and 4%, respectively, of orteronel patients, whereas 4% of placebo patients reported grade 3 AEs of nausea, and 8% hypertension. Grades 2/3 elevation of liver enzymes occurred in 17% and 4% of patients receiving orteronel versus 17% and 8% in the placebo arm, respectively. With orteronel, one (4%) patient experienced transient adrenal insufficiency grade 3, and one (4%) patient developed grade 4 pneumonitis, both responded to treatment.

The investigators stated that this was the first trial, to their knowledge, using an active pharmaceutical ingredient as switch maintenance in mCRPC and that the concept of maintenance

therapy after disease stabilisation with chemotherapy warrants further research in mCRPC.

Gillessen *et al.* Abstract 2500.

### Practice point and future research opportunities

Orteronel showed important anti-tumour activity as a switch maintenance therapy in patients with metastatic castration resistant prostate cancer and non-progressive disease following docetaxel. Maintenance therapy after disease stabilisation with orteronel or another agent warrants further investigation.

## Atezolizumab benefit with increased PD-L1 expression in metastatic urothelial carcinoma

Atezolizumab demonstrated clinical benefit in patients with metastatic urothelial carcinoma (mUC) who had a poor prognosis after progressing on platinum-based chemotherapy, according to phase II trial results reported by Jonathan Rosenberg, Memorial Sloan Kettering Cancer Centre, New York, USA, lead investigator of the IMvigor study. Atezolizumab is a monoclonal antibody that blocks PD-L1 activity and restores the patient's immune response. It has demonstrated activity in mUC, where there is currently a high, unmet need for viable treatments, leading to the granting of breakthrough designation for atezolizumab by the US FDA in 2014 for patients with mUC whose tumour expressed PD-L1.

IMvigor 210 was an international multicentre phase II trial of atezolizumab in patients with locally-advanced or metastatic mUC that enrolled 316 patients who had progressed during or following platinum-based chemotherapy. Atezolizumab was administered at 1200 mg i.v. on the first day of each 21-day cycle until no further clinical benefit was demonstrated; the median treatment duration was 12 (range: 0 to 46) weeks. The co-primary endpoints were overall response rate (ORR), as assessed by central review (RECIST v1.1) and ORR assessed by the investigators using modified RECIST v1.1. Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety. By May 5, 2015, data from 311 patients were evaluable for efficacy and safety. Baseline characteristics showed that the median patient age was 66 years, 78% were male, 62% of patients had ECOG PS 1, and 31% of patients had metastasis to the liver. The patients had been heavily pre-treated; 40% of patients had undergone  $\geq 2$  prior systemic regimens in the metastatic setting and 74% of patients had received cisplatin-based chemotherapy.

PD-L1 expression was prospectively assessed using the SP142 antibody-based IHC assay on tumour cells (TC) and immune cells (IC); however, both the patients and investigators were blinded as to PD-L1 status. The results were evaluated according to the degree of PD-L1 expression. The ORR after atezolizumab significantly improved with higher PD-L1 expression; ORR by RECIST 1.1 was 15% ( $p = 0.0058$ ) in all comers, 18% ( $p = 0.0004$ ) in the IC1/2/3 group (PD-L1 expression  $\geq 1\%$ ) and ORR 27% ( $p = 0.0001$ ) in the IC2/3 group (PD-L1 expression  $\geq 5\%$ ). The median DoR had not been reached at the time of data cut-off, however, at a minimum follow-up of 24 weeks, 92% of responding patients maintained response. Overall, 12 patients achieved complete response (CR), and 35 achieved partial response (PR). In addition, 15 additional unconfirmed RECIST v1.1 CR/PRs were seen. The median PFS at a median follow-up of 24 weeks was 2.1 months across all groups. The OS data are not yet mature but prolonged OS has been noted in patients with higher PD-L1 expression.

Treatment-related adverse events (AEs) of any grade occurred in 66% of patients, with 15% of patients experiencing grades 3/4 AEs including fatigue in 6 (2%) patients. Treatment discontinuation due to an AE was reported in 3% of patients. Studies of atezolizumab as first-line in treatment naive, platinum ineligible patients are ongoing, as is a phase III trial of atezolizumab versus chemotherapy. Rosenberg *et al.* 21LBA.

### Practice point and future research opportunities

IMvigor 210 is the first phase II study of an agent targeting PD-L1/PD-1 in mUC. Classical chemotherapy, with docetaxel as used in the US or vinflunine in Europe, is not very effective in second-line treatment of metastatic bladder cancer. The study data are promising, but it is necessary to await the results of phase III studies (IMvigor and Keynote trials amongst others) before reviewing the current standard of care. It is also important to identify patients with immune cells and /or tumour cells that express PD-L1, since higher PD-L1 expression on immune cells associated with higher overall response rates. Prospective agents currently under evaluation as second-line therapies are atezolizumab that targets PD-L1, pembrolizumab that targets PD-1, and docetaxel/ramucirumab that targets VEGFR-2.

## GYNAECOLOGICAL CANCERS

### ARIEL2: Genetic analysis of the tumour prospectively identifies patients with ovarian cancer most likely to respond to rucaparib

The phase II ARIEL2 trial aimed to identify BRCA mutations in patients with ovarian cancer and to evaluate patient outcome by mutation type. According to Rebecca Kristeleit, University College London, UK at least 50% of high-grade serous ovarian cancer may have homologous recombination deficiency (HRD), of which germline BRCA1 and BRCA2 mutations account for approximately one-third. A next generation sequencing (NGS) tumour-based HRD assay and a novel algorithm were used to assess the tumour BRCA status and to identify HRD tumours likely to respond to rucaparib, an inhibitor of (ADP-ribose) polymerase (PARP).

In part 1 of ARIEL2, patients with platinum-sensitive high-grade serous or high-grade endometrioid ovarian cancer patients with RECIST measurable disease were enrolled and stratified according to HRD tumour subgroups that had been assessed in archival and pre-treatment biopsies: mutated BRCA (BRCA<sup>mut</sup>), BRCA wild-type/high loss of heterozygosity [LOH<sup>high</sup>] (BRCA-like), and BRCA<sup>wt</sup>/LOH<sup>low</sup> (biomarker negative). Rucaparib was given to 204 patients with a median age of 65 (range: 31 to 86) years; 67% of patients had ECOG 0, 96% of patients were high-grade serous, and 43% had received 2 or more prior treatments.

Analysis of efficacy data from 171 patients showed that the primary endpoints, progression-free survival (PFS), and objective response rate (ORR; RECIST v1.1) criteria were met. Patients in the BRCA<sup>mut</sup> and BRCA-like cohorts demonstrated improved PFS and ORR following rucaparib compared to the biomarker negative subgroup: In 39 BRCA<sup>mut</sup>, and 72 BRCA-like patients, PFS was median 285 (95%CI 222, not reached) days and 216 (95%CI 110, 430) days, respectively compared to median PFS of 111 (95%CI 107,166) days in 60 biomarker negative patients. The ORR (RECIST) was 69%, 29% and 13% in the BRCA<sup>mut</sup>, BRCA-like, and biomarker negative cohorts, respectively. The median duration of ORR was 232, 170, and 127 days in the respective cohorts. The authors noted that the ORR by RECIST plus CA125 were similar in patients with germline and somatic BRCA mutations: 80% versus 84%, respectively.

Treatment-related adverse events (AEs) occurring in at least 15% of patients were generally low grade and comprised nausea, fatigue, dysgeusia, transient transaminases, decreased appetite, vomiting, constipation, anaemia, and diarrhoea. Part 2 of the ARIEL2 trial will evaluate the HRD

response signature in 300 additional patients with ovarian cancer receiving  $\geq 3$  prior chemotherapies to assess the utility of the signature, and the response to rucaparib in heavily pre-treated patients. NCT01891344. Kristeleit *et al.* Abstract 2700.

### Practice point and future research opportunities

Rucaparib showed superior efficacy in patients with high-grade serious ovarian cancer and tumours showing HRD that were either BRCA mutated or BRCA-like, and was generally well tolerated.

### Ovarian cancer patients likely to benefit from rucaparib prospectively identified by quantification of genomic loss of heterozygosity

PARP inhibitors target tumour cells with homologous recombination deficiency (HRD), which are thought to result from deleterious BRCA1/2 mutations (BRCA<sup>mut</sup>) or other mechanisms that have not been fully elucidated. HRD displays a common phenotype of genome-wide loss of heterozygosity (LOH), leading Amit Oza, Princess Margaret Hospital, Toronto, Canada, and colleagues to evaluate whether the genomic phenotype of LOH can be used to identify BRCA-like HRD tumours most likely to be sensitive to the PARP inhibitor, rucaparib. They used comprehensive next generation sequencing (NGS)-based tumour genomic profiling to develop an HRD assay, which was used to profile pre-treatment screening biopsies and archival FFPE tumour samples from patients participating in part 1 of the phase II ARIEL2 study; genomic LOH was assessed by sequencing >3,500 evenly-distributed SNPs across the genome, the extent of genomic LOH ( $G_{LOH}$ ) was quantified. The optimal  $G_{LOH}$  cut-off separating overall survival curves was determined and used to pre-specify high and low  $G_{LOH}$  (LOH<sup>high</sup>, LOH<sup>low</sup>) tumours. Known germline BRCA<sup>mut</sup> patient enrollment was capped. Response (by RECIST and GCIG CA-125) in 187 patients was then evaluated.

As of April 8 2015, review of 192 archival and 152 screening tumour samples produced 140 matched pairs from 206 patients with high-grade ovarian cancer enrolled in ARIEL2 part 1, which were profiled using the NGS-based HRD assay. These samples included 20% of enrolled patients were BRCA<sup>mut</sup> (10% germline, 10% somatic), and 7% of patients with genomic alteration in another known HR-pathway gene. Analysis of the matched pairs exhibited similar genomic LOH profiles ( $r=0.86$ ). Consistent with BRCA mutations conferring HRD, BRCA<sup>mut</sup> tumours had significantly higher  $G_{LOH}$  than BRCA wild-type tumours ( $p < 1e^{-7}$ ).

Receiver operating characteristic analysis of  $G_{LOH}$  cut-off showed it could be useful in identifying patients likely to respond to rucaparib (AUC=0.71,  $p < 1e^{-4}$ ). The pre-specified  $G_{LOH}$  cut-off, was used to detect  $LOH^{high}$  tumours in 54% of patients with BRCA wild-type. The response rates varied in patients according to  $G_{LOH}$  cut-off; the response rate following rucaparib in patients with  $LOH^{high}$  tumours was 43% versus 22% in patients with  $LOH^{low}$  tumours ( $p = 0.0072$ ). The authors plan to apply the HRD signature prospectively to the primary analysis of the ongoing portion of the phase II ARIEL2 part 2 and the phase III maintenance studies of rucaparib in patients with high-grade ovarian cancer. NCT01968213. Oza *et al.* Abstract 2701.

### Practice point and future research opportunities

This study demonstrated that a BRCA-like HRD signature assessing genomic LOH can be used to prospectively identify patients with high grade ovarian cancer and tumours expressing BRCA wild-type who may benefit from rucaparib. The signature will be further tested in the ongoing ARIEL3 trial of rucaparib.

## Patients with rare tumours benefit from management by the French National Network dedicated to Ovarian Malignant Rare Tumours (TMRO)

Patricia Pautier, Institut Gustave-Roussy, Villejuif, France, and the PathGyn Group conducted an audit of the prospective collection of clinical data, dedicated multidisciplinary staff decisions, central pathological review, and patient follow-up recorded in the Ovarian Malignant Rare Tumours (TMRO) database since 2011. Rare ovarian tumours (ROT) have such a low incidence that the natural history, prognostic factors and definitive histological diagnostics have not been clearly identified, even though they represent more than 20% of all ovarian cancers. Adding to the complexity of devising treatment strategies is the extreme variability of the characteristics of patients who develop ROT, such as age, histologic subtypes, and the stage at diagnosis. In order to monitor the management of ROT in France, a national network with a dedicated system for referral and information gathering that includes 22 regional expert centers (REC) and 3 national centres was put into place in 2011 to provide equal access to expertise and new treatments for all patients with ROT.

This audit revealed that patients with ROT have increased yearly from 468 patients in 2011 to 1058 patients in 2014. Among patients diagnosed with ROT, 18% represent serous borderline tumours that required pathologist expertise to determine the degree of invasiveness. In 2014, 544 (45%) of

these patients' tumours were reviewed by an expert pathologist and discussed within multi-disciplinary staff in reference centres, which compared favourably to just 166 (25%) patients having access to multidisciplinary staff in 2011. In all, 742 patients with ROT in the 2014 database are managed in REC compared to 294 cases in 2011. National centres were involved in carrying out histological review and induced medical decision modifications for 9% of ROT cases. An increased number of uterine and cervix rare tumours, 216 in all, were also determined by clinicians to need histological and/or clinical advice in 2014. During the years of the network, the number of cases of all tumour types recorded has risen from a total of 468 cases in 2011 to 1058 cases in 2014. The tumour types contained in the network (cumulative number of cases) was stromal and sex-cord tumours (1030), germ cell (534), mucinous borderline (681), mucinous carcinoma (371), clear cell carcinoma (362), serous borderline tumours (556), low grade serous carcinoma (62), carcinoma (180), and small cell carcinoma (37). Research in this field should be vastly aided by the more than 30% of patients who signed informed consent for biology research in 2014. Pautier *et al.* Abstract 2705.

### Practice point and future research opportunities

This audit demonstrates how networks improve disease management and research possibilities. The study clearly shows the patient benefit in management of rare ovarian tumour obtained with the organisation and coordination between reference centres and also the enhanced opportunities for epidemiology and research.



## HEAD AND NECK CANCER

### Cabazitaxel shows clinical benefit in patients with refractory recurrent or metastatic squamous cell carcinoma of the head and neck: Final results of UNICANCER ORL03

Patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) who progress on platinum, anti-EGFR, and taxanes are considered as refractory and offered methotrexate as palliative care. Jerome Fayette, Centre Léon Bérard, Lyon, France, and colleagues evaluated whether cabazitaxel, which has been reported to prolong survival in patients with hormone – refractory metastatic prostate cancer that fail docetaxel, could benefit patients with R/M SCCHN. UNICANCER ORL03 was a multicentre, phase II trial that enrolled 31 patients with R/M SCCHN, ECOG PS 0–2 who progressed after sequential and/or combined platinum, cetuximab and taxanes. All patients received cabazitaxel at 25mg/m<sup>2</sup> every 3 weeks for a maximum of 10 cycles, plus granulocyte colony stimulating factor (G-CSF) support with lenograstim 150µg/m<sup>2</sup>/day, which was administered after each cycle of chemotherapy. Response was assessed every 6 weeks, according to RECIST 1.1 (centralised review). The primary endpoint was non-progression at 6 weeks. Of 31 enrolled patients, data from 29 were evaluated for efficacy; 22 were male, median patient age was 60 (range: 30 to 71) years, 13 (45%) had oropharynx tumours, and 20 (69%) patients had metastatic disease. All had received at least 2 previous lines of chemotherapy and cetuximab.

A total of 81 cabazitaxel cycles were administered and toxicity assessments revealed that the maximum grade of toxicity was 1 to 2 for 31 cycles, grade 3 for 28 cycles, and grade 4 for 12 cycles. The overall toxicity was manageable, although one patient died of toxicity at the 6<sup>th</sup> cycle. The main grade 3/4 toxicity was neutropenia, with 8 (26%) patients having at least one event despite G-CSF use. Treatment-related serious adverse events occurred in 18 of 31 patients including febrile neutropenia in 6 patients resulting in one death.

Data from 29 patients were evaluable for the primary endpoint of non-progression of disease at 6 weeks; by central review, 21 patients had progressive disease but 8 (27.6%) 95%CI 12.7%, 47.2%) patients achieved stable disease, meeting the preplanned endpoint of a minimum of 6 non-progressive patients to consider the drug worthy of further study. Fayette *et al.* Abstract 2800.

#### Practice point and future research opportunities

This trial met its primary endpoint, demonstrating a 27.6% 6-week disease control rate in refractory patients with R/M SCCHN, warranting further investigation of cabazitaxel in this patient population. The toxicity seems acceptable for a heavily pretreated population primarily in poor medical condition.

## Pembrolizumab is safe and shows anti-tumour activity in patients with PD-L1-positive nasopharyngeal carcinoma

High expression of PD-1 has been observed in nasopharyngeal carcinoma (NPC) and PD-1/PD-L1 expression in these tumours is associated with poorer outcome, according to lead investigator Chiun Hsu, National Taiwan University Hospital in Taipei, China. He presented findings from the KEYNOTE-028 non-randomised, multicohort phase Ib trial of pembrolizumab in patients with PD-L1 positive advanced solid tumours showing that one-third of patients showed a measurable decrease in lesion size following pembrolizumab. The KEYNOTE-028 NPC cohort enrolled 27 patients with ECOG performance status 0–1, who had failed prior therapy and had advanced tumours that displayed PD-L1 expression in  $\geq 1\%$  of cells in tumour nests or PD-L1-positive bands in stroma, as determined by immunohistochemistry. Pembrolizumab was given at 10mg/kg every 2 weeks for up to 2 years or until confirmed progression or unacceptable toxicity. The median patient age was 52.0 (range: 18 to 68) years and 63% were Asian. In all, 92.5% of patients had received prior therapies for recurrent and/or metastatic disease and 33.3% had received  $\geq 5$  prior therapies. A preliminary efficacy assessment done after a median follow-up of 12.9 months demonstrated a best overall (confirmed and unconfirmed) response rate of 25.9% (95%CI 11.1, 46.3); one patient achieved complete response, 6 patients had partial response and 14 patients experienced stable disease, lasting a median duration of 5.6 months. The 6-month progression-free survival (PFS) rate was 49.7% and the 12-month PFS rate was 28.9%; median PFS was 5.6 months.

The most frequent all-grade adverse events (AEs) with pembrolizumab, occurring in more than 20% of patients, were fatigue (33%), pruritus (29.6%), nausea ((25.9%), and pyrexia (25.9%). Drug-related AEs occurred in 70.4% of patients and included pruritis (15.9%), fatigue (11.1%), rash (11.1%), maculopapular rash (11.1%), and hypothyroidism (11.1%). At the time of the conference, 8 patients remained on pembrolizumab treatment. (NCT02054806) Hsu *et al.* Abstract 2801.

### Practice point and future research opportunities

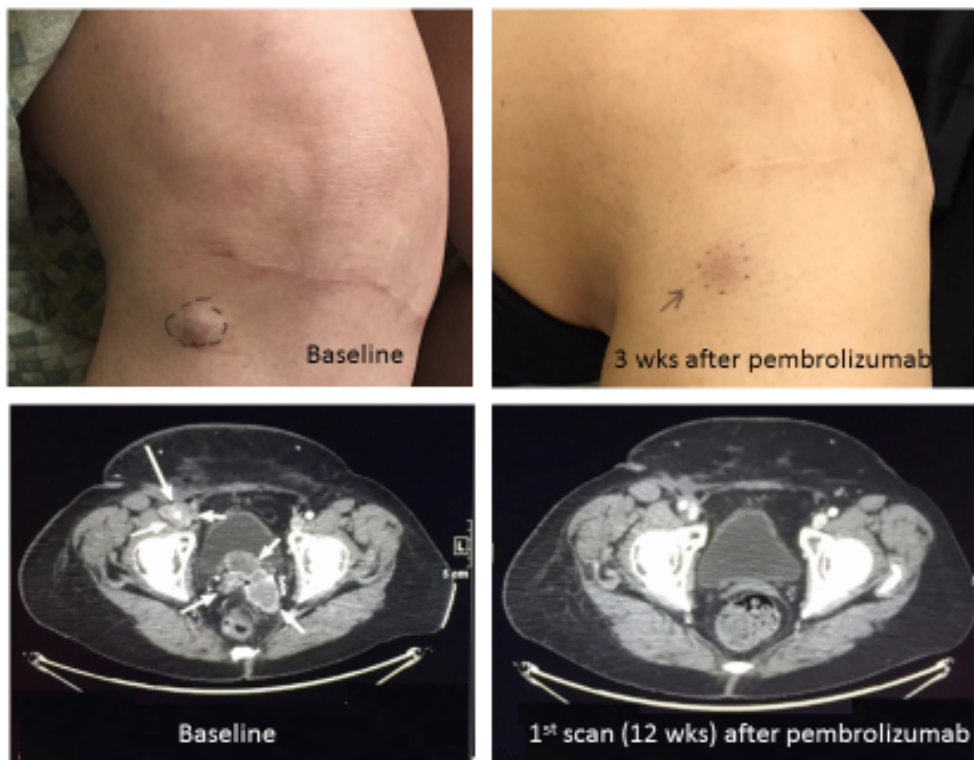
This study represents the first demonstration of robust clinical activity of a PD-1 inhibitor in patients with recurrent metastatic nasopharyngeal carcinoma, which, though rare in Western countries, is a major cancer in parts of Asia. These data show the potential for new approaches to treat this type of cancer, where there are currently limited treatment options, and which carries a poor prognosis.

## IMMUNOTHERAPY FOR CANCER

### Blocking PD1 with pembrolizumab shows promise in patients with Merkel cell carcinoma

The first report of PD-1 blockade in Merkel cell carcinoma (MCC) was made by Paul Nghiem, Fred Hutchinson and Cancer Research Center, Seattle, USA on behalf of colleagues from the Cancer Immunotherapy Trials Network (CITN) and the US NCI's Cancer Therapy Evaluation Program (CTEP). He explained that, although MCC has been historically difficult to treat, MCC tumours express PD-L1, providing an immunotherapeutic target that could make them responsive to PD1 blockade with pembrolizumab. The investigators evaluated pembrolizumab as first systemic therapy in patients with advanced MCC in an open-label, single arm, Simon two-stage trial that could expand to include 24 patients if at least one response was observed among the first 9 patients. The trial enrolled 18 patients with MCC and good performance status, and who were not immune suppressed or did not have autoimmune disease, to receive pembrolizumab at 2 mg/kg every 3 weeks; response (RECIST 1.1) assessments were done every 9 to 12 weeks.

At least one radiologic and clinical response assessment has been done thus far in 10 of the patients enrolled that revealed a 71% response rate. Complete response (CR) was achieved by one patient, and one patient had an unconfirmed CR (uCR). Partial response (PR) was observed in 4 patients and 2 patients have an unconfirmed PR. With pembrolizumab, 2 patients with MCC experienced disease progression and have discontinued the study. The remaining 8 treated patients have not yet had initial scans; however, 3 patients with clinically measurable disease have shown regression of clinically evaluable lesions following pembrolizumab, although visceral disease status awaits radiologic evaluation.



**Caption:** A 70 year old woman developed metastatic Merkel cell carcinoma (MCC) involving the abdomen and pelvis as well as right thigh skin metastases (one lesion shown at top left). Pelvic metastases (bottom left, indicated by arrows) led to bladder compression and urinary frequency.

One week after an initial dose of pembrolizumab (2mg/kg) urinary frequency resolved and the lesions on the leg regressed. The leg lesion (top right) was biopsied at week 3 and showed a robust lymphocytic infiltrate with no residual MCC tumor cells by immunohistochemistry.

A restaging scan at week 13 (after 4 doses of pembrolizumab) showed complete resolution of the posterior wall mass of the urinary bladder (bottom right) and overall a >50% regression per RECIST. She continues to receive treatment on trial without side effects and her tumours continue to decrease in size.

**Credit:** Paul Nghiem.

Adverse events included grade 4 myocarditis in one patient after the first dose, and one patient had grade 4 transaminase elevation after receiving 2 doses; both patients improved with steroid

treatment after the study drug was discontinued. Interestingly, both of these patients demonstrated favourable tumour responses, with one patient showing regression of skin metastases, while the other patient continues to show an ongoing PR of extensive visceral. The authors noted that 8 of the 10 patients evaluated following pembrolizumab monotherapy as the first systemic intervention have shown evidence (5 confirmed and 3 unconfirmed by subsequent scans) of response to PD-1 pathway blockade and 3 of 3 additional patients with clinically evaluable metastases have shown clinical regression of tumours (prior to first scan). The investigators speculated that this high response rate may partly be due to the immune response to antigens in the tumour from the polyomavirus that often drives MCC. Of the 18 patients enrolled, 14 continue to receive anti-PD-1 on trial. The authors concluded that reporting these data may benefit patients with this aggressive cancer by encouraging accelerated clinical testing of PD-1 blocking agents in MCC. Nghiem *et al.* Abstract 22LBA.

### Practice point and future research opportunities

While these data are still early, these results are very promising, especially in such a rare and difficult-to-treat disease where there is a high medical need for novel therapies. The findings include a high objective response rate and the responses are especially noteworthy given the difficulty in treating MCC, which often evades the patient's immune response, making durable responses to chemotherapy in the metastatic setting difficult to achieve with progression-free survival rates of around just 90 days commonly observed. PD-1 blockade is a promising treatment that warrants further investigation in Merkel cell carcinoma, among other cancer types.

### Significant PD-L2 expression detected in varied human tumour types

Jennifer H. Yearley, Merck & Company Inc., Kenilworth, USA discussed the significance of PD-L2 expression and how it may allow broader use of PD-1 targeting agents in the treatment of an expanded range of human tumour types. Biomarker screening by immunohistochemistry (IHC) done prior to administering PD-1 targeting agents to determine whether the tumour type is a candidate for treatment with these agents has revealed some PD-L1–negative patients that have responded to PD-1 targeted therapies, possibly via tumour expression of the other known ligand, PD-L2. Therefore, Yearley and colleagues investigated the expression of PD-L2 in different tumour types and evaluated the potential role it may play regarding clinical responsiveness to anti-PD-1 therapies. They used a novel IHC assay for PD-L2 on groups of archival tissue from 7 human tumour types, including renal cell carcinoma (RCC), bladder carcinoma, melanoma, non-small cell

lung cancer (NSCLC), head and neck squamous carcinoma (HNSC), triple-negative breast cancer (TNBC), and gastric carcinoma. Sample sizes of the groups evaluated ranged from 22 tissue samples in TNBC to 94 samples in NSCLC, with a median sample size of 71 samples per tumour type. The findings of PD-L2 IHC staining was also compared with PD-L2 mRNA levels, as determined using the Nanostring platform, and with results obtained using PD-L1 IHC staining.

This study demonstrated that PD-L2 expression within the tumour microenvironment can be significant in these 7 tumour types. A significant association was determined between the extent and distribution of PD-L2 IHC labelling and the extent and distribution of PD-L1 IHC labeling (range:  $p = 0.0012$  to  $p < 0.0001$ ). PD-L2 expression was also shown to significantly correlate with levels of PD-L2 mRNA in the tumour samples, (range:  $p = 0.0037$  to  $p < 0.0001$ ).

Discordant expression was also observed: Individual tumour samples showed PD-L1 expression in the absence of PD-L2, while other tumour samples showed the reverse. Therefore, the authors suggest that screening for both biomarkers may best guide the selection in PD-1 axis targeting agents. They also summarised that PD-L2 expressed within human tumours in the absence of PD-L1 may provide an alternate target for agents directed to the PD-1 pathway, and at least partially account for PD-L1–negative patients having a positive clinical response to anti-PD-1 targeted therapies. Yearly *et al.* Abstract 18LBA.

### Practice point and future research opportunities

Treatment with drugs targeting the PD-1 axis has resulted in groundbreaking improvements in clinical response in multiple human cancers. Biomarker screening prior to initiation of PD-1 axis-targeted treatments has focused on evaluation of tumour expression of PD-L1, a known ligand of PD-1. However, this study showed another ligand, PD-L2, is expressed within human tumours and determined the prevalence and distributional properties of PD-L2 in multiple cohorts of archival human tumours and has shown significant expression of PD-L2 in 7 cancer types. These findings suggest some patients populations may benefit from anti-PD-1 targeted therapies blocking both interactions but who might not experience benefit from an agent targeting just PD-L1. PD-L2 expression may also, in part, explain the response to anti-PD-1 agents reported in PD-L1 negative patients screening for both ligands is warranted.

### Pneumonitis reported during anti-PD-1/PD-L1 therapy has varied subtypes



Pneumonitis is a rare but potentially fatal side effect of immune checkpoint antibodies targeting the PD-1/PD-L1 pathway, according to lead author Jarushka Naidoo, Johns Hopkins, Baltimore, USA, who also pointed out that the clinical and radiographic features of immune-related pneumonitis associated with these agents are poorly described. This study reviewed clinicopathological data from 653 patients receiving an anti-PD-1/PD-L1 monoclonal antibody, either alone or in combination, while participating in a clinical trial from 2009 to 2014. Chest computed tomography (CT) scans of all patients were independently assessed by 2 radiologists by describing the radiologic features throughout clinical course of pneumonitis, grading each case as mild/moderate/severe, and reassessing the CT scans together to create a 'consensus read'.

In all, 36 (6%) patients reported an adverse event (AE) of pneumonitis within 11 different therapeutic protocols. The median age of these patients was 63 (range: 34 to 78) years, and 23 (64%) were former/current smokers. Most patients developing pneumonitis received PD-1/PD-L1 therapy as part of a combination; 14 (39%) patients received anti-PD-1/PD-L1 monotherapy whereas 22 (61%) patients received combination therapy. Of these, 33 (92%) patients received an anti-PD-1 monoclonal antibody, 3 (8%) received an anti-PD-L1 monoclonal antibody.

Standard radiologic assessment criteria identified 5 distinct subtypes of pneumonitis: Chronic obstructive pneumonia (COP)-like was reported in 7 (19%) patients, ground-glass opacifications (GGO) in 13 (36%), hypersensitivity-type in 7 (19%), interstitial-type in 4 (11%) patients and pneumonitis not-otherwise-specified (NOS) was identified in 5 (14%) of pneumonitis patients. Subtypes of pneumonitis were found to generally associate with the site of primary cancer: COP-like pneumonitis was reported in 6 patients with lung cancer but just one patient with haematologic malignancies and GGO was most often seen in melanoma ( $p = 0.025$ ). Pneumonitis hypersensitivity-type, interstitial-type and NOS were distributed across cancer subtypes. COP-like pneumonitis compared to other subtypes, showed a trend towards association with the development of grade 3plus toxicity ( $p = 0.052$ ) and with the requirement for more than one type of immunosuppression ( $p = 0.093$ ). The authors summarised that pneumonitis reported as an AE following anti-PD-1/PD-L1 therapies may display a variety of radiologic appearances and these radiologic subtypes may associate with the primary cancer site, with COP-like pneumonitis possibly more clinically aggressive. Naidoo *et al.* Abstract 503.

### Practice point and future research opportunities

These findings may help clinicians to identify the rare but potentially fatal adverse event of pneumonitis following anti-PD-1/PD-L1 therapies, and have particular relevance in lung cancer and melanoma, where these agents have been recently approved for use in the clinic.

## Immune infiltrate changes with PD1 inhibition associate with response in patients with melanoma

Ricardo Vilain, Melanoma Institute Australia, Sydney, Australia, reported on changes observed in tumoural PD-L1 expression and tumour-associated immune cell flux in melanoma patients undergoing treatment with immune checkpoint inhibitors. Although checkpoint inhibitors have demonstrated improved survival in metastatic melanoma patients by disrupting PD-L1/cytotoxic T-cell PD1 signalling, little else is known about these treatments. To characterise PD-L1 expression in patients undergoing treatment with checkpoint inhibitors, this study analysed 49 tumour biopsies from 24 patients with unresectable AJCC stage III/IV metastatic melanoma; 21 biopsies each had been collected prior to (PRE) and within two months of commencing treatment (EDT), whereas 7 were taken upon disease progression (PROG).

The best response (RECIST or iRC criteria) following pembrolizumab or nivolumab was correlated with the histomorphological and immunohistochemical analysis; a complete response (CR) was achieved by one patient, 6 patients showed partial response (PR), and 9 patients had stable disease. In the PRE biopsies, intra-tumoural and peri-tumoural density of PD1-positive T-cells was 8.1-fold higher ( $p = 0.0142$ ) and 6.8-fold higher ( $p = 0.0098$ ), respectively, in responding patients. Furthermore, the PRE intra-tumoural and peri-tumoural density of PD1-positive T-cells significantly associated with the degree of tumour shrinkage on radiology ( $r = -0.356$ ,  $p = 0.0090$ ) and ( $r = -0.442$ ,  $p = 0.0035$ ), respectively. Analysis of the EDT biopsies revealed a significant influx of intra-tumoural CD3+, CD8+ and CD68+ macrophages during treatment in responders that was not seen in non-responders. Also, during treatment, responders showed a higher distribution of PD-L1 expression on tumour cells ( $p = 0.0554$ ) and on macrophages ( $p = 0.0379$ ). Analysis of biopsies from patients progressing during treatment revealed that PD-L1 expression was present in both the tumour and macrophage cell components and a trend for increased intra-tumoural and peri-tumoural macrophage density was observed.

The authors concluded that the higher numbers of PD1-positive T-cells in the PRE biopsies of responders suggests the active suppression of the immune response, which was disrupted by anti-PD1 therapies and that the increased PD-L1 expression seen in the EDT biopsies of responders

likely reflects disengagement of the PD-L1/PD1 axis, reactivation of PD1positive T-cells and increased interferon- $\gamma$  production. The biopsies from the patients with progressive disease suggest the acquisition of resistance to PD1 inhibition, and the lack of changes in PD-L1 expression or T-cell infiltrates suggests other mechanisms are involved in immune escape. Vilain *et al.* Abstract 3305.

### Practice point and future research opportunities

This analysis of biopsies taken prior to and during treatment with pembrolizumab and nivolumab reflected changes in PD-L1 expression and changes in the cells in the tumour environment. Patients responding to treatment showed an association with higher PD-1 expression on T cells surrounding the tumour prior to treatment and increased macrophage infiltration plus increased PD-1-positive expression on tumour cells and macrophages during treatment, whereas PD-L1 was uniformly expressed on tumour and macrophages in the biopsies of patients progressing on treatment. These intriguing results should be confirmed and expanded upon in analyses of larger number of biopsy samples from larger trials.

## LUNG CANCER

### Highly specific rovalpituzumab tesirine shows clinical benefit as single agent in second and third-line treatment of SCLC

M. Catherine Pietanza, Memorial Sloan Kettering Cancer Center, New York, USA reported results from a phase I/Ib multicentre study showing that the antibody-drug conjugate, rovalpituzumab tesirine, had strong clinical activity as second- and third-line treatment of patients with small-cell lung cancer (SCLC). This study was the first-in-human trial of rovalpituzumab tesirine, which comprises a humanised monoclonal antibody to the delta-like protein 3 (DLL3), a dipeptide linker, and a pyrrolobenzodiazepine dimer toxin. DLL3 is a Notch ligand that is not expressed in normal tissue but is overexpressed in SCLC tumour-initiating cells. Clinical activity was strongest in the subset of patients with tumours having high expression of DLL3, the drug target.

The trial enrolled 79 patients previously treated for progressive SCLC; 33 patients were female and the overall median age was 62 (range 44 to 81) years. Rovalpituzumab tesirine was given to 34 patients every 3 weeks (Q3W) and to 45 patients Q6W in escalating doses of 0.05, 0.1, 0.2, 0.4 and 0.8mg/kg until dose limiting toxicities were observed. Maximum tolerated doses (MTD) of 0.2mg/kg Q3Wx3 cycles and 0.3mg/kg Q6Wx2 cycles were taken further to the Ib expansion cohorts. Pharmacokinetic data revealed a longer-than-expected half-life, encouraging a Q6W schedule. The investigators developed a DLL3 antibody, which was used to assess antigen expression in 48 archived tumour specimens, with 33 (69%) being DLL3-positive.

The combined clinical benefit rate was 66% in the 29 patients with confirmed DLL3-positive tumours and who received the MTD; of these, 10 (34%) patients had partial response and 9 (31%) patients achieved stable disease. The duration of response in patients with confirmed responses at the recommended phase 2 dose (RP2D) of 0.3mg/kg Q6W was 178+ (range: 58 to 266+) days. Of particular interest were the significant response rate of 17% observed among 35 patients receiving the MTD in the third-line setting, where no standard-of-care currently exists. This response rate was further enriched to 42% in 15 patients who were DLL3-positive.

The most commonly reported treatment emergent adverse events (TEAEs) of any grade occurring in ≥20% of patients were fatigue (47%), dyspnoea (24%), nausea (24%), and decreased appetite (22%). Serious TEAEs included serosal effusions reported in 11 (14%) patients and

thrombocytopenia in 3 (4%) in patients. Phase II studies are being planned. NCT01901653 Peitanza *et al.* Abstract 7LBA.

### Practice point and future research opportunities

Currently, for SCLC there is no standard third line treatment, so rovalpituzumab tesirine is likely to fulfill an unmet need for these patients. Rovalpituzumab tesirine demonstrated substantial single-agent anti-tumour activity and durability in patients with relapsed or refractory DLL3-positive SCLC, which may also have identified a predictive biomarker, DLL3, that is associated with drug efficacy, allowing for a targeted treatment in SCLC. Additional, larger trials are warranted.

### Mutation profile in stage III NSCLC shows prognostic value for progression-free survival

Angela Boros from Institut Gustave Roussy, Villejuif, France, presented results on behalf of colleagues who evaluated the prognostic value of specific gene alterations, including EGFR, KRAS, BRAF mutation, or ALK rearrangement by reviewing data from 190 consecutive patients receiving chemotherapy or radiotherapy with a curative intent, the standard for stage III non squamous non-small cell lung cancer (NSCLC); the prognostic value of alteration in these genes had to date been unknown. The investigators collected paraffin embedded tissue blocks from these patients and DNA was extracted for gene mutation analysis by next generation sequencing; ALK, ROS1 and RET rearrangements were detected by FISH analysis. The survival analysis used Kaplan–Meier methods, log-rank test, and Cox proportional hazards models that adjusted for performance status (0 versus  $\geq 1$ ), stage (IIIA versus IIIB) and whether patients received thoracic surgery. Radiotherapy was delivered at a median dose of 66 Gy (range: 46 to 70 Gy). Platinum-based chemotherapy was administered concomitantly to 108 patients and as induction/consolidation treatment in 170 patients; 15 patients received no chemotherapy.

The prognostic value of specific gene alterations was investigated in 78 patients having evaluable material; 20 (26%) were female, 47 (60%) were current smokers, 40 (51%) had adenocarcinoma and there were 47 stage IIIA and 31 IIIB cases. The most prevalent mutations identified in this cohort were KRAS (15%), EGFR (12%), BRAF (5%; 3 mutations per 66 gene positive samples), NRAS 3% (1 of 32), CTNNB1 3% (1 of 32), and PI3KCA 2% (1 of 58). All 65 samples containing HER2 showed no mutation. FISH was positive for ALK rearrangement in 5% (3 of 56) of NSCLC

samples but no alteration in ROS1, RET, HRAS and AKT1 was found in 32 NSCLC samples in which the test was performed.

The association with patient outcome was evaluated at a median follow-up of 3.1 years and showed specific gene alterations associated with significantly worse progression-free survival (PFS); the 11 patients with EGFR mutated or ALK-positive had poorer PFS of median 0.8 year, 95%CI 0.6, 0.9 year and 17 patients with other mutations had 0.5 year, 95%CI 0.4, 0.8 year compared to 50 patients with wild-type genotype who demonstrated median PFS of 1 year; 95%CI 0.9, 1.3 (multivariate hazard ratio (HR) 1.8 and 2.8, respectively;  $p = 0.004$ ). No significant difference in OS was noted: median OS was 2.4 (95%CI 1.3; NR) for patients with EGFR/ALK, 1.1 (95% CI 0.6, 2.5] for patients with other mutations and 1.9 [95%CI 1.5; 2.5] for patients with wild type genes ( $p = 0.23$ ). OS associated significantly only with the dose of radiotherapy received, HR 0.5 [95%CI 0.3, 1.0 ( $p = 0.04$ ). Boros *et al.* Abstract 3000.

### Practice point and future research opportunities

Specific gene alterations may associate with a poorer progression-free survival in patients with stage III NSCLC treated by chemoradiotherapy or radiotherapy. The prognostic and/or predictive value of these alterations should be further evaluated in larger populations.

## Prevalence of gene mutations in patients with NSCLC: Results from the ETOP Lungscape Project

Lead author Keith Kerr, Aberdeen Royal Infirmary, Aberdeen, UK, presented findings from the ETOP Lungscape Project which assessed whether multiplex mutation analysis could predict the prevalence and clinical implications of gene mutations in patients with resected stage I–III non-small cell lung cancer (NSCLC). The investigators used samples from 2709 patients with resected stage I–III NSCLC with clinical data contained in the ETOP Lungscape Biobank to evaluate the prevalence of mutations and determine their association to clinicopathological features and patient outcome, including overall survival (OS), recurrence-free survival (RFS), and time to relapse (TTR). DNA was extracted from FFPE samples and assessed for gene mutation using Fluidigm technology, a microfluidics-based multiplex PCR platform. Mutant allele detection sensitivity is  $>1\%$  for most of the ~150 (13 genes) mutations covered in the multiplex test. Local quality assurance was verified in a central collaborating laboratory, where samples were standardised before genomic analysis.



Study findings represented multiplex testing evaluation of 1502 (55.4%) patient samples. The patients had a median age of 66.3 years and 64.0% were male; adenocarcinoma occurred in 48.3% of patients and 42.9% had squamous cell carcinoma. Smoking status was 7.2% never, 34.2% current and 52.7% former smokers, and the disease stage was: IA in 22.2%, IB in 26.0%, IIA in 17.2%, IIB in 12.2%, IIIA in 20.3%, and IIIB in 2.1% of cases. FFPE samples dated from 2005 to 2008 but recently extracted DNA quality and quantity was generally good, yielding average of 2.63 µg DNA per case; only 38 (1.4%) cases failed quality control and were excluded from study; 95.1% of included cases allowed the complete panel of mutations to be tested.

The most commonly occurring mutations (prevalence) were KRAS (23.2%), MET (6.3%), EGFR (5.1%) and PIK3CA (4.9%); NRAS and BRAF mutation were found in 11 cases (0.7%), and HRAS in 9 (0.6%). Just one case of AKT1 and MYD88 mutations were identified and no ERBB2, FLT3, JAK2 or KIT mutations were found. EGFR and KRAS mutations were found predominantly in patients with adenocarcinoma, with Exon 19 deletion being the most common EGFR mutation (56.8%) and G12C the most prevalent KRAS mutation (45.0%). EGFR mutations were found most often in females, and never smokers. PIK3CA mutations were most prevalent in patients with squamous cell carcinoma and were detected in 60% of patient samples. MET mutations had a similar prevalence across squamous cell and adenocarcinoma cases.

No difference in OS, RFS, or TTR was found between patients with or without EGFR, KRAS, MET and PIK3CA mutations. Kerr *et al.* Abstract 3001.

### Practice point and future research opportunities

Accurate assessment of specific genetic mutations in NSCLC, especially identification of driver mutations, is crucial in determining the appropriate personalised therapy. The Lungscope Project demonstrated that archival FFPE samples from patients with NSCLC can provide adequate material for multiplex mutation analysis and allow molecular characterisation in a predominantly European, clinically annotated cohort.

### Atezolizumab out performs docetaxel in patients with NSCLC and tumours expressing PD-L1 in the phase II POPLAR trial

Johan Vansteenkiste, University Hospitals Leuven, Belgium presented findings from the randomised, phase II POPLAR trial of atezolizumab, a PD-L1 antibody, in the second- and third-line settings in unselected patients with metastatic or locally advanced non-small cell lung cancer



(NSCLC). POPLAR randomised 287 previously treated patients to receive atezolizumab (n = 144) or docetaxel (n = 143); atezolizumab was administered at 1200 mg i.v. every 3 weeks and docetaxel at 75 mg/m<sup>2</sup> i.v. every 3 weeks. The primary objective was estimated overall survival (OS) by intention-to-treat (ITT) analysis and by PD-L1 expressions subgroups. Secondary objectives included estimated progression-free survival (PFS), objective response rate (ORR), and duration of response by ITT and by PD-L1 expression. The median patient age was 62 years and one-third of the patients received atezolizumab or docetaxel as third-line therapy.

Across all PD-L1 expression levels, as determined using the SP142 IHC assay, the ORR was 15% with both treatments. The value of patient selection by PD-L1 expression was demonstrated by the higher response rates seen in patients with the highest PD-L1 expression; in patients with high PD-L1 levels on tumour cells/tumour-infiltrating immune cells (TC/IC 3), the median PFS was 7.8 versus 3.9 months, for atezolizumab and docetaxel, respectively (HR 0.60; 95% CI 0.31, 1.16). The ORR was 38% with immunotherapy versus 13% with chemotherapy. In this group, the median OS was 12.6 versus 9.7 months and the median PFS was 2.7 versus 3.0 months, for atezolizumab and docetaxel, respectively. In the subgroup of patients without PD-L1 expression TC/IC 0, no difference in OS was observed and was 9.7 months for both arms. However, PFS favoured docetaxel and was 1.7 versus 4.1 months in the atezolizumab and docetaxel arms, respectively. The ORR was 8% with atezolizumab versus 10% with docetaxel in this subgroup of patients without PD-L1 expression.

The profile of adverse events was in line with data reports from other PD-1/PD-L1 checkpoint inhibitors. Although atezolizumab patients received longer median treatment of 3.7 versus 2.1 months for docetaxel, fewer patients had treatment-related grade 3/4 adverse events (AEs); 11% of atezolizumab patients compared with 39% of docetaxel patients experienced an AE. A randomised phase III study of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC who failed platinum therapy is ongoing. NCT01903993. Vansteenkiste *et al.* Abstract 14LBA.

### Practice point and future research opportunities

Atezolizumab may change treatment strategies for patients with refractory PD-L1 positive lung cancer; atezolizumab was granted breakthrough therapy designation for patients with PD-L1-positive NSCLC in February 2015. Efficacy, demonstrated by the response rate, correlated with the degree of PD-L1 expression on tumour and tumour-infiltrating immune cells.

## Atezolizumab is a new addition to rapidly changing treatment paradigms in NSCLC

Lead investigator Benjamin Besse of the Institut Gustave Roussy, Villejuif, and the Paris Sud University, Paris, France reported findings from the BIRCH trial that evaluated the clinical efficacy of atezolizumab as first- and subsequent line, monotherapy in patients with advanced non-small cell lung cancer (NSCLC). Atezolizumab is a humanized antibody targeting PD-L1 that inhibits PD-L1/PD-1 interaction while preserving the interplay between PD-L2/PD-1, which potentially preserves peripheral immune homeostasis.

BIRCH was an open-label, single-arm phase II study of atezolizumab administered either as first-line or as subsequent second- or third-line in patients with advanced NSCLC. Participants were from 200 centres in 19 countries worldwide and selected for high PD-L1 expression by immunohistochemistry (IHC) done on both archival and fresh tissue samples. Patients with stage IIIB/IV or recurrent NSCLC but no active central nervous system metastases were enrolled. In all, 659 patients were treated and evaluated for efficacy and safety. Atezolizumab was given at 1200 mg i.v. at 3-week intervals as first-line to 142 patients with no prior chemotherapy (cohort 1) until disease progression or unacceptable toxicity, as second-line to 271 patients who had received one prior platinum therapy, and to 254 patients who had undergone 2 or more prior chemotherapy regimens (cohort 3) until loss of clinical benefit was seen. Patients in cohorts 2 and 3 had progressed after chemotherapy. All enrolled patients showed PD-L1 expression at high levels on tumour cells (TC) or tumour-infiltrating immune cells (IC) as TC2/3 or IC2/3 or on both cell types. Patient characteristics were balanced across cohorts; the median age was 64 years, 35% were ECOG PS 0, 28% had squamous NSCLC and 17% of patients were never-smokers. EGFR and KRAS mutation was identified in 327 and 177 patients overall, respectively.

BIRCH met its primary efficacy endpoint, overall response rate (ORR), according to IRF per RECIST v1.1 for defined subgroups. Key secondary endpoints were duration of response (DoR), progression-free survival (PFS) by IRF and investigator, ORR by investigator, overall survival (OS) and safety. At a minimum follow-up of 6 months, 61% of responses were ongoing. Tumour shrinkage was observed in up to 27% of patients and who expressed PD-L1 at higher levels ( $p = 0.0001$ ). The median treatment duration across all cohorts was 4.2 (range: 0 to 15) months. The ORR in cohort 1 was 19% and 17% in cohorts 2 and 3 in patients with TC2/3 or IC2/3 expression.

Stronger response was seen in patients with higher expression; ORR rates were 26%, 24% and 27% in cohorts 1, 2, and 3 in patients with PD-L1 expression of level TC3 or IC3.

OS data are not yet mature; however, 6-month OS was achieved by 76%, 75%, and 71% of patients in cohorts 1, 2, and 3 having TC2/3 or IC2/3 expression levels and by 79%, 82% and 80% of patients in cohorts 1, 2, and 3 having TC3 or IC3 expression levels, respectively. At median follow-up of 8.8, 7.9, and 8.6 months median OS was 14 months, not reached (NR) and NR across cohorts 1, 2, and 3, respectively. Improved PFS also mirrored higher PD-L1 expression; 6 month PFS rates were 29, 39, 31 with PD-L1 expression of TC2/3 and IC2/3 and 48%, 46% and 34% in patients with TC3 or IC3 levels in cohorts 1, 2, and 3, respectively.

The safety profile was consistent with that demonstrated in other studies; treatment-related adverse events (TRAEs) occurred in 11% of patients overall and TRAEs leading to study discontinuation occurred in 5% of patients. All cause adverse events (AEs) grades 3/4 were reported in 38% of patients. The most commonly reported AEs were fatigue and nausea, which occurred in 18% and 10% of patients, respectively. Data analysis according to EGFR mutation status is ongoing. NCT02031458. Besse *et al.* Abstract 16LBA.

### Practice point and future research opportunities

The PD-L1 antibody atezolizumab showed remarkable activity in a large number of patients regardless of the line of treatment in the BIRCH trial. Atezolizumab benefit associated with the extent of PD-L1 expression on tumour cells and tumour infiltrating cells, with the highest activity seen in patients demonstrating expression on both cell types, showing the utility of selecting patients based on PD-L1 expression for anti-PD-L1 therapy. While first-line treatment with atezolizumab in patients with PD-L1 high expressing tumours is promising, the combination of atezolizumab with platinum-based chemotherapy remains an attractive option and is currently being investigated in large randomized phase III trials.

### Nivolumab improves benefit over docetaxel in patients with non-squamous NSCLC: Long-term update from CheckMate

The risk of death was decreased by 28% with nivolumab versus docetaxel for patients with previously treated non-squamous non-small cell lung cancer (NS-NSCLC), according to lead investigator Leora Horn from the Vanderbilt-Ingram Cancer Centre who presented updated findings from the phase III, open-label CheckMate-057 study. CheckMate randomised 582 patients with

advanced NS-NSCLC who had progressed on platinum-based doublet chemotherapy to nivolumab at 3 mg/kg i.v. every 2 weeks (n = 292) or docetaxel at 75 mg/m<sup>2</sup> i.v. every 3 weeks (n = 290). The median patient age was 62 years and the majority had an ECOG performance status of 1. Prior maintenance with bevacizumab, pemetrexed, or erlotinib was allowed, as was tyrosine kinase inhibitor (TKI) therapy for those with known EGFR mutations or ALK translocation; 40% and 38% of patients in the nivolumab and docetaxel arms, respectively, had received prior maintenance therapy. In the nivolumab arm, 15% of patients were EGFR-positive and 4% were ALK-positive compared with 13% and 3% in the docetaxel group. A median 6 doses versus 4 of nivolumab were administered versus a median 4 doses of docetaxel.

At a minimum follow-up of 17.2 months, the overall survival (OS) rate with nivolumab was 39% versus 23% with docetaxel; median OS with nivolumab was 12.2 versus 9.4 months with docetaxel, HR 0.72; 95% CI 0.60, 0.88 (p < 0.001). The 1-year progression-free survival (PFS) rates were 19% and 8% and the objective response rates (ORR) were 19% and 12%, with nivolumab and docetaxel, respectively. Patients receiving nivolumab demonstrated median time to response of 2.1 months versus 2.6 months with docetaxel. The median duration of response (DoR) was 17.2 months with nivolumab versus 5.6 months with docetaxel.

In 455 (78%) patients with quantifiable PD-L1 expression, a greater benefit with nivolumab over docetaxel was seen in patients with ≥1% staining; in patients with PD-L1 expression ≥1%, ORR of 31% and a DoR of 16 months was seen in 123 nivolumab patients versus an ORR of 12% and a DoR of 5.6 months in 123 patients receiving docetaxel. Patients with the highest expression of PD-L1 (≥10%), demonstrated an ORR with nivolumab of 37%, with a median DoR of 16 months compared with an ORR of 13% and a DoR of 5.6 months with docetaxel, odds ratio 4.1 (95% CI 1.8, 10.1). However, patients with expression <1% had an ORR of 15% with docetaxel (n = 101) compared with 9% with nivolumab (n = 108).

Adverse events (AEs) occurred significantly less frequently with nivolumab: Rates of all-grade AEs were 69% and 88%, with nivolumab and docetaxel, respectively, and grade 3/4 AEs occurred in 10% of nivolumab patients compared with 54% for docetaxel. The most common grade 3/4 AEs with nivolumab were fatigue, nausea, and diarrhoea, which each occurred in 1% of patients. With docetaxel, 27% of patients had grade 3/4 neutropenia versus 0 in the nivolumab arm. Toxicity-related discontinuations occurred in 5% of patients receiving nivolumab versus 15% of patients receiving docetaxel. These data were simultaneously published in the NEJM [Borghaei *et al.* N Engl J Med 2015; 373:1627-1639]. Horn *et al.* Abstract 3010.

### Practice point and future research opportunities

The longer-term survival results for nivolumab in advanced, non-squamous non-small cell lung cancer support the potential for this agent in treating lung cancer patients.

### KEYNOTE-001 shows robust activity with pembrolizumab in patients with previously treated advanced NSCLC

Jean-Charles Soria, Institut Gustave Roussy in Villejuif, France reported that nearly 30% of previously treated non-small cell lung cancer (NSCLC) patients with elevated PD-L1 expression had objective responses following treatment with 2 mg/kg of pembrolizumab, and the rate increased to 40% at a 10 mg/kg dose. The investigators conducted the phase I KEYNOTE-001 trial in previously treated and treatment-naïve patients with advanced or metastatic NSCLC; however, the data presented at the ECC involved the subset of 449 previously treated patients. Investigators studied the safety and efficacy of pembrolizumab at either 2 mg/kg (n = 55) or 10 mg/kg (n = 238) administered every 3 weeks or and 10 mg/kg given every 2 weeks (n = 156). The evaluation included patients with PD-L1–positive and negative tumours. Patient characteristics showed even distribution between men and women among the groups, a median age of 62 to 63 years, and 82% non-squamous histology. A majority (53%) of the 394 patients treated at the 10 mg/kg dose had received 3 or more prior lines of therapy, as compared with 36% of the patients receiving 2 mg/kg. The overall response rate (ORR) at both dose levels was 18.7% (95% CI 15.2, 22.6). The response rate increased with increasing PD-L1 expression in patients treated with either dose. Median overall survival (OS) for all patients treated with the 10 mg/kg dose was 11.1 months and median progression-free survival (PFS) was 3.0 months. However, in the subgroup of patients with PD-L1 expression  $\geq 50\%$ , OS increased to median 15.5 months and median PFS increased to 5.8 months. The 6-month OS was 63% in all patients treated with 10 mg/kg of pembrolizumab compared with 71.6% for PD-L1–positive patients. The 6-month PFS increased from 34.0% in patients overall to 49.9% for those with PD-L1 levels  $\geq 50\%$ . In this subgroup, 74.2% of patients had some degree of tumour reduction with pembrolizumab, as compared with 51.7% of patients who had less than 50% PD-L1 tumour expression.

Similar safety was seen across the two doses of pembrolizumab; grade 3/4 adverse events (AEs) occurred in 10.5% of patients, and 4.0% of patients discontinued due to a treatment-related AE.

Three treatment-related deaths from cardiorespiratory arrest, interstitial lung disease, and respiratory arrest occurred.

The phase II/III randomised KEYNOTE-010 trial is ongoing and compares pembrolizumab at 2 mg/kg and 10 mg/kg doses administered every 3 weeks with docetaxel in patients with previously treated NSCLC. NCT01905657. Soria *et al.* Abstract 33LBA.

### Practice point and future research opportunities

In the pivotal KEYNOTE-001 trial, efficacy with pembrolizumab in patients pretreated for NSCLC was shown to increase in patients having 50% or greater PD-L1 tumour expression. Accelerated approval for pembrolizumab in patients with metastatic NSCLC whose tumours express PD-L1 (determined by an FDA-approved test) with disease progression on or after platinum-containing chemotherapy was granted in October 2015 by the US FDA. Patients with tumours harbouring EGFR or ALK genomic aberrations should have experienced disease progression on FDA-approved therapy specific for these aberrations prior to receiving pembrolizumab.

### Rociletinib is active in patients with EGFR mutant NSCLC and a history of CNS metastases

Andrea Varga, Institute Gustave Roussy, Villejuif, France presented preliminary findings from a subgroup of patients with advanced EGFR-positive non-small cell lung cancer (NSCLC) progressive disease after  $\geq 1$  EGFR tyrosine kinase inhibitor (TKI), participating in the TIGER-X trial of rociletinib. TIGER-X is a phase I/II open-label study wherein an overall response rate of 67% has previously been reported for T790M positive patients [Soria 2014]. Rociletinib (CO-1686) is a novel, oral, irreversible TKI with activity against the activating mutations, L858R and Del19, plus the dominant acquired resistance mutation, T790M, but not against wild-type EGFR.

The subgroup comprised 170 patients with a history of CNS disease that was stable and asymptomatic; patients developing progressive disease (PD) while on rociletinib were allowed to continue, if deemed clinically beneficial by the investigator. The primary endpoint was RECIST overall response rate (ORR).

As of 16 March 2015, a total of 401 patients had received therapeutic dose levels of rociletinib (500, 625 and 750 mg BID) including 170 patients in the CNS disease subgroup, who showed a RECIST response rate of 41%. Among these patients, 42 have continued rociletinib post-progression. Patients continuing rociletinib for at least 14 days post progression demonstrated



average treatment duration beyond PD of 89 days (range: 14 to 336 days). In this cohort, 22 patients also received brain radiation and continued rociletinib treatment (held on radiation days only) for an average of 120 days (range: 22 to 336 days) after PD.

The cohort of patients with a history of CNS disease showed a similar safety profile to the overall TIGER-X patient population, with hyperglycemia, diarrhoea and nausea reported most commonly. Additional efficacy data are not yet mature for this subgroup. Varga *et al.* Abstract 3009.

### Practice point and future research opportunities

Rociletinib has demonstrated activity by RESIST and has safely been administered in patients with a history of CNS disease, which is associated with a poorer prognosis. Continued rociletinib use after disease progression and CNS radiation suggests an ongoing systemic benefit to these patients. The role of rociletinib in NSCLC patients with CNS involvement will be further evaluated in the ongoing TIGER clinical development programme. Data from the TIGER-X and TIGER-2 trials supported an application to the European Medicines Agency for patients with pretreated EGFR T790M-mutant NSCLC, which was granted an accelerated assessment. The US FDA granted Breakthrough Therapy designation for rociletinib as treatment for mutant NSCLC in patients with the T790M mutation after progression on EGFR-directed therapy in 2015; the New Drug Application is set for review by the Oncologic Drugs Advisory Committee in 2016.



## MELANOMA

### Baseline genetic heterogeneities do not alter superior clinical benefit seen with cobimetinib/vemurafenib over sole vemurafenib in advanced BRAFV600-mutated melanoma: Updated results from co-BRIM

Grant McArthur, Peter MacCallum Cancer Centre in Melbourne, Australia reported updated efficacy results from the ongoing phase III placebo-controlled coBRIM study of patients with advanced BRAFV600-mutated melanoma, together with findings from an analysis of outcome according to individual mutations present in tumour tissue taken prior to treatment. Cobimetinib is an extremely selective allosteric small molecule inhibitor of MEK that was used with vemurafenib, which targets BRAF, to achieve co-inhibition of BRAF and MEK. Findings from coBRIM previously reported [ESMO 2014] showed treatment-naïve BRAFV600 mutation-positive patients with advanced melanoma receiving cobimetinib plus vemurafenib demonstrated significant improvement in progression-free survival (PFS) and objective response rate (ORR).

Results presented at the ECC from an analysis done at 14.2 months of follow-up also favoured cobimetinib/vemurafenib over vemurafenib monotherapy; the median PFS was 12.3 months with combination compared to 7.2 months with sole vemurafenib, HR 0.58. The ORR was 70% versus 50%, and the complete response (CR) rates were 16% versus 11% with cobimetinib/vemurafenib versus vemurafenib, respectively.

The impact of baseline tumour heterogeneity, including BRAFV600 copy number, RAS and other genetic sequence variants that could drive resistance, on clinical outcome was also evaluated. Tumour samples collected prior to treatment were analysed by targeted deep-sequencing to a median coverage of 3600×. Variant allele frequency was calculated as a ratio of the variant allele to total read depth at the V600 codon and hotspots in 17 additional oncogenes.

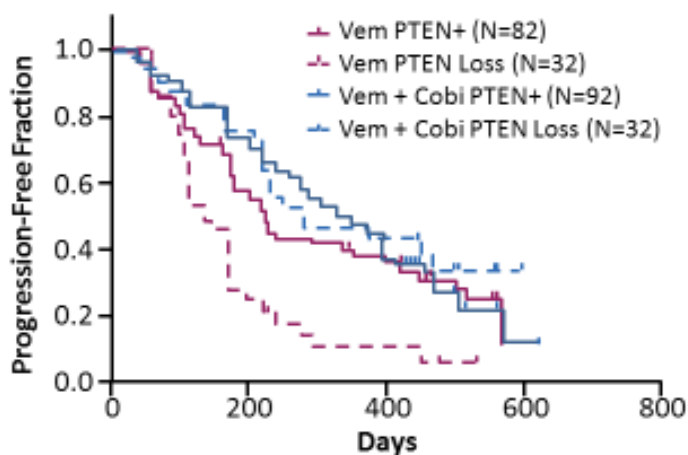
Immunohistochemistry (IHC) was used to assay PTEN loss and Cox proportional hazards modelling was used to determine the association between biomarker parameters and PFS that was observed until the data cut-off of 16 January 2015. This analysis showed that the advantage seen with combination treatment was consistent across several mutation types, those that might be predicted to induce resistance. Cobimetinib/vemurafenib showed clinical benefit across every patient subgroup evaluated, including patients with BRAFV600K and BRAFV600E mutation, where

median PFS was 12.4 months, HR 0.52 (95% CI 0.27, 1.02) and 10.6 months, HR 0.64 (95% CI 0.49, 0.83), respectively.



## Addition of Cobimetinib to Vemurafenib Overcomes the Negative Impact of PTEN Loss on PFS

### Progression-Free Survival Based on PTEN Expression



PTEN+: H-score  $\geq 50$   
PTEN Loss: H-score  $< 50$

HR, Vem PTEN loss v Vem + Cobi  
1.6; 95% CI, 0.96-2.8

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**Caption:** coBRIM – Addition of cobimetinib to vemurafenib overcomes the negative impact of PTEN loss on progression-free survival.

**Credit:** Grant McArthur

The presence of co-mutation in oncogene hotspots and tumour suppressor genes known to mediate resistance to BRAF or MEK inhibition, including RAS, RTK, and PTEN, at allele frequencies of  $>3\%$  (median 8.6%) had no impact on PFS in either arm, with the exception of PIK3CA mutation or PTEN loss. Loss of PTEN expression was associated with shorter PFS in patients receiving vemurafenib monotherapy, as compared to patients with intact PTEN; HR 1.6 (95% CI 0.96, 2.8). However, loss of PTEN did not affect PFS in patients receiving cobimetinib/vemurafenib. The authors suggest these data support the combination of cobimetinib/vemurafenib as the new standard of care for patients with advanced BRAFV600-mutated melanoma. NCT01689519. Mc Arthur et al. Abstract 25LBA.

### Practice point and future research opportunities

The most common mechanism of acquired resistance to the BRAF inhibitor vemurafenib is reactivation of cell growth via the MAPK pathway through MEK; administering a BRAF inhibitor and MEK inhibitor together in the first-line setting turns off both proteins, thereby increasing pathway inhibition and delaying the development of resistance that is observed with BRAF inhibition alone. This updated data from co-BRIM shows that simultaneous inhibition with cobimetinib/vemurafenib improved progression-free survival over BRAF inhibition with vemurafenib and also was unaffected by baseline genetic heterogeneities. These results may represent practice changing findings in patients with advanced BRAF V600 mutation-positive melanoma.

### Promising clinical benefit with ribociclib and binimetinib combination in patients with NRAS-mutant melanoma confirmed in dose finding study

Promising preliminary anti-tumour activity has been reported from a simultaneous blockade of activation of the MAPK signalling pathway by targeting MEK with binimetinib and CDK4/6 with ribociclib in advanced NRAS-mutant melanoma [Sosman et al. ASCO 2014], leading Carla Van Herpen, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands and colleagues to conduct this phase Ib/II, open-label study of ribociclib plus binimetinib in patients with NRAS-mutant melanoma. The phase Ib segment aimed to determine the maximum-tolerated dose (MTD)/recommended phase 2 dose (RP2D) of the combination and secondary objectives included safety, pharmacokinetics, and preliminary efficacy. Ribociclib/binimetinib doses up to 300/45 mg have been assessed and 450/45 mg is currently being tested; 2 dosing schedules were assessed, a 28-day cycle of ribociclib once daily (QD) for 21 days plus binimetinib twice daily (BID) continuously and a 21-day cycle of ribociclib QD plus binimetinib BID for 14 days per cycle.

Regarding the 28 day cycle, 22 patients with ECOG PS 0/1/2 in 41%, 50%, and 9% of patients received one of 4 ribociclib/binimetinib combination dose levels: 9 patients received DL1 of 200/45 mg, 3 patients had DL2 of 250/45 mg, 4 patients received DL3 at 300/30 mg, and 6 patients received DL4 of 300/45 mg. The MTD for the 28-day cycle was determined to be DL1, based upon the following dose limiting toxicities: One patient in the DL1 cohort experienced grade 3 acute renal injury, and one patient at DL3 suffered fatal intracranial bleeding. In the DL4 cohort one patient each had grade 4 anaemia, grade 4 asymptomatic creatinine phosphokinase elevation (CPK), and grade 3 oedema plus grade 4 atrial fibrillation. Overall, the safety profile following exposure to this combination was consistent with single-agent results; the most commonly reported treatment-

related toxicities included elevated CPK, anaemia, rash, nausea, oedema, diarrhoea, elevated creatinine, elevated phosphate, neutropenia, and vomiting.

Promising efficacy results were reported, with 5 (23%) patients achieving partial response (PR), and 4 (18%) patients achieving unconfirmed PR. Stable disease occurred in 9 (41%) patients. Preliminary median progression-free survival was estimated at 6.2 (95%CI 3.7, NE) months. Several patients reported early tumour shrinkage that was accompanied by major symptomatic improvement. No patients currently remain on the 28-day treatment cycle treatment and assessment of the 21-day cycle is ongoing in 22 patients with an MTD as yet undetermined. Van Herpen et al. Abstract 3300.

### Practice point and future research opportunities

Determination of the recommended phase 2 dose and optimal dosing schedule is ongoing for the combination of ribociclib and binimetinib, which continues to show promising preliminary antitumour activity in patients with NRAS-mutant melanoma.

## Anti-PD-1 combined safely with radiotherapy in patients with metastatic melanoma

Previous reports suggest that radiotherapy may induce an abscopal immune response, possibly mediated by the release of tumour antigens and subsequent immune recognition, which could be enhanced by immunotherapy. Therefore, Elizabeth Liniker, Melanoma Institute Australia, Sydney, Australia and colleagues evaluated data from 32 patients with unresectable stage III/IV melanoma who received PD1 therapy, consisting of either nivolumab or pembrolizumab, and current or sequential radiotherapy to determine the safety and clinical outcomes of patients having immunotherapy plus radiotherapy. At the start of PD1 therapy, 16 patients had a median of 4 brain metastases, 21 (54%) had an elevated LDH, and 29 (74%) patients had M1c disease. Various radiotherapy regimens were delivered, including radiotherapy to extracranial sites in 27 (69%) patients, 4 (10%) patients had stereotactic radiotherapy to brain metastases, 4 (10%) patients underwent whole brain radiotherapy, and 4 (10%) patients received a combination of these treatments. After beginning PD1 therapy, the median time to radiotherapy was 8.5 (range: 28 to 185) days.

Although no complete response (CR) by RESIST was observed, 9 patients achieved partial response (PR), and 5 patients had stable disease. A total of 82 metastases were irradiated; of

these, 25 were clinically or radiologically progressing on PD1 therapy at the start of radiotherapy; subsequently, 3 (12%) of these patients achieved CR, 7 (28%) achieved PR, and 5 (20%) patients experienced progression. In the cohort of patients with brain metastases, the median progression-free survival (PFS) was 2.5 months and overall survival (OS) was 6.8 months, whereas patients without brain metastases had PFS of 4.1 months and OS of 16.4 months.

The investigators concluded that radiotherapy plus PD1 therapy does not increase acute extracranial toxicity; however, since one patient with multiple small asymptomatic brain metastases receiving PD1 therapy and concurrent whole brain radiotherapy experienced potential delayed neurotoxicity, they suggest that potential neurotoxicity with cerebral radiotherapy requires investigation. One patient experienced cerebral radionecrosis 3 months after stereotactic radiotherapy that responded to bevacizumab and steroids. One patient had disproportionate cerebral oedema. The investigators are continuing to evaluate irradiated and non-irradiated lesion-specific and site-specific (intracranial and extracranial) response rates. Liniker et al. Abstract 3302.

### Practice point and future research opportunities

These results suggest that radiotherapy may be effective for patients with lesions that progress on PD1 therapy and that they can be safely co-administered. Although no excess acute extracranial toxicity was observed in this small study, the potential for neurotoxicity with cerebral radiotherapy requires further investigation.

## Analysis of key patient subgroups in CheckMate 067 shows consistent superior progression-free survival with combined nivolumab plus ipilimumab versus sole nivolumab or ipilimumab in treatment-naïve patients with advanced melanoma

Lead author James Larkin, Royal Marsden Hospital, London, UK, presented an analysis of predefined key subgroups that included patients with poor prognostic factors from the phase III CheckMate 067, which demonstrated significantly improved progression-free survival (PFS) with combined ipilimumab and nivolumab over either as monotherapy in advanced melanoma. CheckMate randomised 945 treatment-naïve patients to receive nivolumab at 3 mg/kg plus placebo, or nivolumab at 1 mg/kg plus ipilimumab at 3mg/kg Q3W for 4 weeks followed by nivolumab at 3mg/kg Q2W, or sole ipilimumab at 3mg/kg Q3W for 4 weeks plus placebo until disease progression or unacceptable toxicity.

The analysis demonstrated enhanced patient outcome with combination treatment across all subgroups, according to BRAF mutation status, age, disease stage, and baseline LDH levels. In the overall population, median PFS was 11.5 months with combination nivolumab/ipilimumab, versus 2.9 months with ipilimumab, HR 0.42 ( $p < 0.00001$ ), and 6.9 months with nivolumab, HR 0.57 versus ipilimumab ( $p < 0.00001$ ).

Consistently longer PFS was seen combined nivolumab plus ipilimumab or with nivolumab monotherapy than with ipilimumab in subgroups defined by BRAF mutation status. Median PFS was 11.7 months with the combination among patients with a BRAF mutation and 11.2 months among patients with wild-type BRAF compared with 7.9 versus 5.6 with nivolumab and 2.8 versus 4.0 months with ipilimumab in BRAF mutated and BRAF wild-type, respectively. In patients less than 65 years, PFS was 11.7, 5.5, and 2.8 months in the combination, nivolumab, and ipilimumab cohorts, respectively. Median PFS was 11.1, 12.7 and 2.9 months in the 65 to 75 year cohort, versus not reached, 5.3, and 4.0 months in patients over 75 years with combination, nivolumab, and ipilimumab, respectively. Regarding disease stage, patients with tumours staged M0/M1a/M1b demonstrated median PFS of 15.5, 9.3, and 4.2 months versus patients with M1c tumours, wherein median PFS was 8.5, 5.4, and 2.8 months with combination, nivolumab, and ipilimumab, respectively. Analysis of treatment according to baseline LDH showed patients below the ULN had median PFS of 14.0, 10.2, and 4.0 versus patients with measurements above ULN, who benefited the least from all treatments, by demonstrating median PFS of 4.2, 2.8, and 2.6 months with combination, nivolumab and ipilimumab, respectively.

The safety profile across subgroups was consistent with that observed in the overall safety population; the overall incidence of drug-related adverse events grade 3/4 was 55.0% with combined nivolumab/ipilimumab, 16.3% with nivolumab, and 27.3% with ipilimumab. Larkin et al. Abstract 3303.

### **Practice point and future research opportunities**

The combination of nivolumab and ipilimumab showed prolonged progression-free survival in patients with previously untreated advanced melanoma that was consistent across key subgroups that included patients with poor prognostic factors, such as increased baseline LDH. The safety profile with the combination therapy suggests that it may be used safely in a broad range of clinical settings.



## The majority of lesions are metabolically inactive in patients with metastatic melanoma receiving long-term anti-PD-1 therapy

Ben Kong, Westmead Hospital, Sydney, Australia presented findings on behalf of colleagues from an analysis of metabolic activity in individual lesions from patients with metastatic melanoma following long-term treatment with the anti-PD1 antibodies, nivolumab or pembrolizumab. In all, 27 patients received computed tomography (CT) or 18-F Fluorodeoxyglucose positron emission tomography (FDG-PET) scans after one year of treatment (median 15.2, range: 9.5 to 35.0 months). The best overall radiological response (ORR) and response rates at time of PET scanning was determined using standard immune related response criteria (irRC) and classification of the presence of FDG-PET metabolic activity was done by visual inspection, with lesions subsequently being characterised as PET positive or negative based upon the metabolic activity of individual lesions identified on CT. Unexpected PET positive foci were included in the lesion-specific analysis even if not visible on prior CT and biopsy or surgery was performed where clinically indicated to investigate the cause of unexpected or atypical lesions.

Following anti-PD1 treatment, the best ORR was complete response (CR), which was seen 9 (33%) patients; 11 (41%) patients achieved partial response (PR), 6 (22%) patients had stable disease (SD) and one (4%) patients experienced progressive disease (PD). At the time PET scans were taken, 8 (29.6%) patients were in complete CT response and achieved CR, another 8 (29.6%) showed PR, 4 (14.8%) patients had SD and 7 (25.9%) showed PD.

CT scans taken prior to PET scanning identified 62 individual lesions, of which 34 (55%) lesions were PET positive and 28 (45%) were PET negative; 5 additional PET positive lesions were identified by PET which were not noted on CT. Patients demonstrating a response who had not progressed per irRC demonstrated lesions that were negative by PET in 63% of cases. However, just 14% of lesions were negative by PET in patients showing PD. In the cohort of 8 patients achieving CR, 6 (75%) had negative PET scans, whereas 2 (25%) patients had PET positive scans; however biopsies excluded melanoma in both cases and instead confirmed lymphocytic infiltrate and granuloma. In the cohort of 8 patients having PR, 4 (50%) patients had no PET positive lesions. The authors concluded that PET may be no more sensitive than CT for recurrence detection in patients with a radiological complete response, and suggested that false positive results on PET may be due to treatment related granulomatous reactions, and biopsies of



unexpected or atypical lesions should be considered to confirm or exclude disease progression.  
Kong et al. Abstract 3304.

### Practice point and future research opportunities

Findings from this study show that the majority of residual disease on CT is metabolically inactive in patients with melanoma who show a prolonged response to anti-PD1 therapy. In this series, PET was no more sensitive than CT in lesion detection. Lesions detected on PET but not CT should be biopsied.

### MASTERKEY-265 safety data reveals no dose limiting toxicities with talimogene laherparepvec and pembrolizumab in unresectable stage IIIB-IV melanoma and supports phase III trial

Findings presented by lead investigator Georgina V. Long, University of Sydney in Sydney, Australia revealed that the combination of the attenuated oncolytic virus talimogene laherparepvec (T-VEC) and the immune checkpoint inhibitor pembrolizumab passed an early safety evaluation for the treatment of unresectable melanoma. PD-1/PD-L1 inhibitors, such as pembrolizumab, have previously demonstrated activity in advanced melanoma, and T-VEC is an oncolytic herpes simplex virus type 1 that has been engineered to replicate selectively in tumour cells and express human GM-CSF.

Safety was assessed using data from phase Ib of the MASTERKEY-265 study, which enrolled 21 treatment-naïve patients with unresectable stage III/IV melanoma and injectable lesions; patients with clinically active brain metastases, active herpetic skin lesions, or a history of herpetic infection complications were excluded. An intralesional T-VEC injection at doses up to 4 mL per treatment was injected into cutaneous, subcutaneous, or nodal lesions at 106 PFU/mL (day 1), 108 PFU/mL (day 22), then Q2W. Pembrolizumab was added from day 36 at 200 mg i.v. Q2W. Treatment continued until complete response (CR) or progressive disease (PD) occurred, no injectable lesions (T-VEC only) remained, or for up to 2 years. The primary endpoint was dose-limiting toxicities (DLTs), which were assessed during weeks 0 to 6. Data cut-off was 6 weeks after the last patient had the first pembrolizumab dose. The 21 patients enrolled from December 2014 to March 2015 had a median age of 8.0 years, 62% were female, 90% of patients had ECOG PS 0, 48% had stage IIIB-IVM1a, 52% had stage IVb/c, and approximately 20% had BRAF-positive melanoma.

All patients received one or more doses of both T-VEC and pembrolizumab. No DLTs were reported over a treatment duration of median 13.1 weeks that included a median 7 of doses of T-VEC, and treatment duration was median 10.1 weeks that included a median 5 doses of pembrolizumab. No patients discontinued therapy due to an adverse event. All patients experienced a treatment-emergent adverse event (TEAE) that was mostly grades 1/2; the grade 3 TEAE rate was 29% and no grade 4 TEAEs occurred. The only grade 3 TEAEs occurring in more than one 1 patient were anaemia and rash, each occurring in 2 patients; rash occurred following the first pembrolizumab. The most common TEAEs were rash (57%), pyrexia (38%), fatigue (29%), chills (24%), nausea (19%), pruritis (19%), diarrhoea (19%), vomiting (14%), headache (14%), and arthralgia (14%). One patient had a grade 1 TEAE of cytokine release syndrome. One patient died of shock related to progressive disease and not to treatment. NCT02263508. Long et al. Abstract 24LBA.

### **Practice point and future research opportunities**

T-VEC and pembrolizumab have favourable and non-overlapping adverse event profiles and the combination was well tolerated at full dose with no dose limiting toxicities in patients with unresectable stage IIIB-IV melanoma. Efficacy data are not yet available but the combination may have favourable anti-tumour activity. The phase Ib study supports the initiation of the randomised phase III part of the study evaluating the efficacy and safety of the combination compared with pembrolizumab monotherapy.

## NEUROENDOCRINE TUMOURS

### Progression-free survival prolonged with everolimus in patients with advanced lung/gastrointestinal neuroendocrine tumours

Findings from the pivotal RADIANT-4 study presented by lead investigator James Yao, University of Texas MD Anderson Cancer Centre, Houston, USA, showed that everolimus provided a significant 52% risk reduction in patients with advanced, progressive lung/gastrointestinal (GI) neuroendocrine tumours (NET) who also achieved progression-free survival (PFS) that was 7.1 months longer than PFS in similar patients receiving placebo. Everolimus is a mTOR inhibitor that has been approved in advanced pancreatic NET; however, advanced, non-functional NET of lung/GI origin remains an area of significant unmet medical need wherein the efficacy and safety of everolimus had not yet been determined.

RADIANT-4 was a randomised, placebo-controlled, double-blind, multicentre, phase III trial of everolimus versus placebo that was conducted in 302 patients with advanced, progressive, well-differentiated, non-functional lung/GI NETs. Patients were stratified by tumour origin, WHO performance status (PS), and prior somatostatin analogue treatment, and then randomised 2:1 to receive best supportive care (BSC) plus either everolimus at 10 mg per day (n=205) or placebo (n=97). Patient median age was 63 years, 53% of patients were female, and 76% were Caucasian. Disease status was grade 1/grade 2 in 64% and 35% of patients, respectively, and WHO PS was 0 in 74% or 1 in 26% of patients. The most commonly reported tumour sites were the lung in 30%, and the ileum in 24% of patients; 53% versus 56% of patients in the everolimus and placebo groups respectively had received prior somatostatin analogue therapy, 26% versus 24% had received chemotherapy and 22% versus 20% had undergone previous loco-regional radiotherapy.

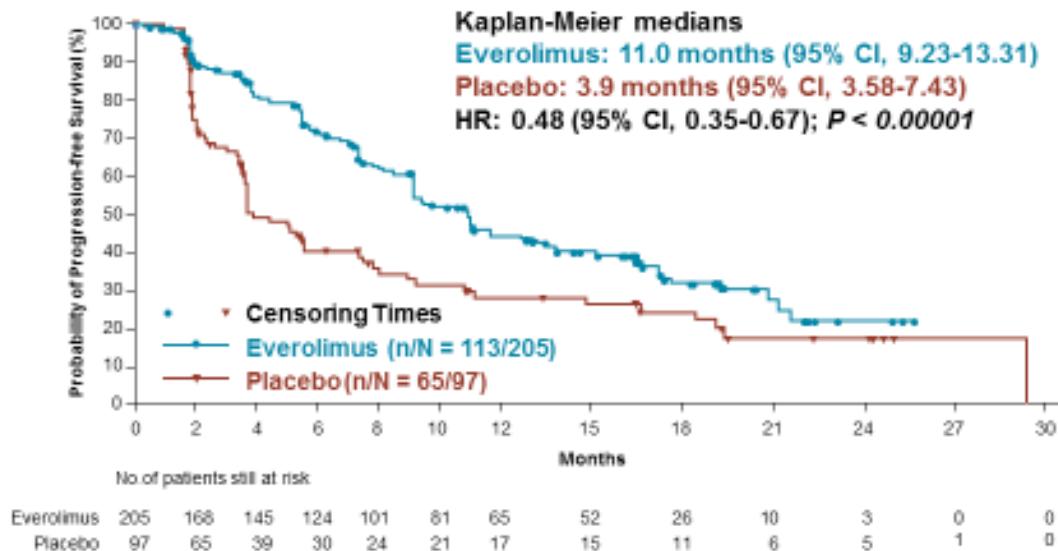
Progression-free survival (PFS) assessed by central radiology review (modified RECIST 1.0), the primary endpoint, was median 11.0 (95% CI 9.2, 13.3) months with everolimus compared to 3.9 months (95% CI 3.6, 7.4) months with placebo, HR 0.48; 95% CI 0.35, 0.67 ( $p < 0.001$ ).

Investigator-assessed PFS was consistent with the central review; PFS with everolimus was 14.0 (95% CI 11.2, 17.7) months compared to 5.5 (95% CI 3.7, 7.4) months with placebo, HR 0.39; 95% CI 0.28, 0.54 ( $p < 0.001$ ). Subgroup PFS analyses by stratification factors also were consistent with these assessments.

## Primary Endpoint: PFS by Central Review

ECCO

**52% reduction in the relative risk of progression or death with everolimus vs placebo**



*P*-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.

**Caption:** Treatment of patients with advanced lung and gastrointestinal neuroendocrine tumours was associated with a 2.8 fold improvement in median progression-free survival from 3.9 months to 11 months.

**Credit:** James Yao

Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety. ORR by central review, showed no complete response (CR) but 4 (2%) everolimus patients and one (1%) placebo patient showed partial response (PR). DCR was 82% with everolimus versus 65% with placebo. Progressive disease was reported for 9% of everolimus patients compared to 27% of patients receiving placebo. Tumour response was unknown in the remaining patients. A pre-planned interim OS analysis showed a trend toward improved OS favouring everolimus that did not reach statistical significance, HR 0.64, 95% CI 0.40, 1.05 ( $p = 0.037$ ).

The most commonly reported adverse events (AEs) grades 1/2 included stomatitis, diarrhoea, peripheral oedema, fatigue, and rash. Grades 3/4 AEs of diarrhoea and anaemia were reported by 9% versus 2% and 5% versus 2% of patients receiving everolimus and placebo, respectively. Grades 3/4 abdominal pain was reported for 5% of each treatment arm and stomatitis was reported by 7% of patients receiving everolimus.

Results from all 4 RADIANT studies support the use of everolimus in grade 1 and 2 disseminated and progressive NET, regardless of primary tumour origin, and the authors noted that findings from the RADIANT-4 study may guide treatment of patients with advanced, non-functional NETs of the lung or GI tract. Yao *et al.* Abstract 5LBA.

### Practice point and future research opportunities

RADIANT-4 is the first large, placebo-controlled, prospective phase III trial to unequivocally demonstrate clinical benefit with everolimus versus placebo. These findings may represent practice-changing data that support the efficacy and safety of everolimus across the broad spectrum of neuroendocrine tumours.

## NETTER-1: Novel peptide receptor radionuclide therapy shows clinical benefit in patients with midgut neuroendocrine tumours

According to lead investigator Philippe Ruszniewski, Beaujon Hospital, Clichy, and Paris Diderot University in Paris, France, Lutathera® has shown promising results in thousands of patients with advanced midgut neuroendocrine tumours (NETs). Lutathera is a <sup>177</sup>Lu-Dotatate peptide receptor radionuclide therapy (PRRT) that targets somatostatin receptors, which are overexpressed in about 80% of NETs, to deliver cytotoxic radiation directly to the tumour. The NETTER-1 trial was

the first phase III multicentre, stratified, randomised, controlled trial to compare Lutathera to octreotide LAR, the current standard of care, in patients with inoperable, progressive, somatostatin receptor positive midgut NETs. The primary endpoint was progression-free survival (PFS) by RECIST 1.1 criteria and secondary objectives included objective response rate (ORR), overall survival (OS), time to progression (TTP), safety, tolerability and health-related quality of life. NETTER-1 enrolled 230 patients with grade 1–2 metastatic midgut NETs that were randomised in a 1:1 ratio to receive Lutathera in 4 intravenous doses at 7.4 GBq administered every 8 weeks together with renal protection consisting of an amino acid solution infusion or octreotide LAR at 60 mg by deep intragluteal injection every 4 weeks.

After a median 30 months of follow-up, analysis of data from 229 patients in the intent to treat (ITT) population revealed the median PFS with Lutathera was not reached compared with 8.4 months with octreotide LAR, HR 0.209; 95% CI 0.129, 0.338 ( $p < 0.0001$ ); Professor Ruzniewski remarked that the estimated PFS derived from the immature data placed the median PFS at approximately 40 months with Lutathera. ORR was 19% in the Lutathera arm; 95% CI 11%, 26% versus 3% with octreotide LAR; 95% CI 11%, 26 ( $p < 0.0004$ ). One patient receiving Lutathera achieved complete response (CR) and 18 patients showed partial response (PR) compared to no CR and 3 PR with octreotide LAR. Stable disease was achieved by 77 (66%) patients and by 70 (62%) patients in the respective cohorts, while progressive disease was experienced by 5 (4%) Lutathera patients and by 27 (24%) octreotide LAR patients. The interim OS analysis of the ITT population revealed a trend toward improved OS ( $p < 0.0186$ ) that did not reach statistical significance. This ongoing trial will continue to follow survival parameters until the data mature.

At the time of the interim analysis, 13 patients receiving Lutathera and 22 octreotide LAR patients had died. The number of centrally confirmed disease progressions or deaths was 23 in the Lutathera group compared to 67 with octreotide LAR. The safety profile in NETTER was consistent with the safety information generated in the phase I and II clinical trials. Serious adverse events (SAEs) with Lutathera included lymphocytopenia, reported in 3 patients, and thrombocytopenia, neutropenia, pancytopenia and bicytopenia, which each occurred in one patient. There were 2 SAEs of acute kidney injury and one case of renal failure. The authors suggest that Lutathera may also have clinical benefit in other types of NETs, for example, pancreatic and bronchial.

Ruzniewski *et al.* Abstract 6LBA.

### Practice point and future research opportunities

These findings confirmed data from phase I and II trials and provide reasonable evidence that Lutathera represents a major advance in treatment of patients with advanced midgut NETs, wherein treatment options are limited for patients who progress following first-line somatostatin analogues. Midgut NETs comprise 20 to 45% of overall NETs, which has an estimated incidence of 47,300 in Europe; moreover incidence has been seen to increase steadily over the past years, most probably due to improved diagnosis. These results showed that Lutathera was superior to octreotide LAR for the treatment of advanced midgut NETS and may be practice changing for the treatment of these patients.

## SARCOMAS

### Phase III sarcoma study final results show patient benefit with trabectedin but not in overall survival

Final overall survival (OS) findings from a phase III trial conducted by Shreyaskumar R. Patel, MD, Anderson Cancer Center, Houston, USA, and colleagues were consistent with the interim analysis in showing no significant advantage with trabectedin over dacarbazine in advanced leiomyosarcoma or liposarcoma. The open-label trial, randomised 518 patients with a variety of soft tissue sarcoma histologies in a 2:1 ratio; 345 patients received 1.5 mg/m<sup>2</sup> of trabectedin and 172 patients received 1.0 g/m<sup>2</sup> of dacarbazine once every 3 weeks until disease progression or unacceptable toxicity. Patients in the trabectedin arm also were given 20 mg of i.v. dexamethasone as premedication.

The primary endpoint was OS; an analysis done after 381 deaths had occurred at a median 21-month follow-up showed the OS with trabectedin was median 13.7 months compared with 13.1 months with dacarbazine, HR 0.93; 95% CI 0.75, 1.15 (p = 0.492). However, the difference in median progression-free survival (PFS) was significant; median trabectedin PFS was 4.2 versus 1.5 months with dacarbazine, HR 0.55; 95% CI 0.44, 0.70 (p <0.001). Patients received a median of 4 trabectedin treatment cycles compared with 2 dacarbazine cycles and the median duration of response was 6.5 versus 4.2 months, respectively, HR 0.47 (p = 0.14). The objective response rates were 9.9% with trabectedin versus 6.9% with dacarbazine and the clinical benefit rate (response plus stable disease rate) was 34% and 19%, respectively. While OS findings were consistent across a planned subgroup analysis with that of the overall study population (HR 0.93), multivariate analysis showed that OS was improved by trabectedin for patients receiving just one prior line of chemotherapy versus ≥2 and for those with an ECOG PS of 0 versus 1 (p < 0.05).

Adverse events (AEs) with trabectedin were higher overall versus dacarbazine and included nausea (73% versus 49%), fatigue (67% versus 51%), neutropenia (49% versus 29%), increased ALT levels (45% versus 6%), vomiting (44% versus 21%), anaemia (39% versus 29%), constipation (36% versus 28%), increased AST levels (35% versus 5%), and diarrhoea (34% versus 23%). Grade 3 AEs with the highest frequency in the trabectedin arm versus dacarbazine, respectively, were increased ALT levels (25% versus 1%), neutropenia (21% versus 11%), anaemia (14% versus 11%), and increased AST levels (12% versus 0%). With trabectedin, 16% of



patients had grade 4 neutropenia compared with 10% in the dacarbazine group. Treatment-related discontinuation rates were 12.6% and 7.7% with trabectedin and dacarbazine, respectively. There were treatment-associated deaths within 30 days of the last dose among 2.1% of patients receiving trabectedin but none in the dacarbazine arm; the deaths were related to sepsis/septic shock in 3 patients, while rhabdomyolysis/sepsis, renal failure, renal failure/cardiac arrest, and multi-organ failure each occurred in one patient.

The authors pointed out factors that could have confounded the OS results: 70% of patients in both arms received subsequent therapies and the median time to initiation of subsequent therapy was significantly prolonged with trabectedin compared with dacarbazine (6.8 months versus 3.5 months, HR 0.53;  $p < 0.0001$ ). The possibility that this had a confounding impact was supported by a sensitivity analyses of OS, which showed a consistent favourable trend with trabectedin. These results have also recently been published in the JCO. Patel *et al.* Abstract 3403.

### Practice point and future research opportunities

Whereas the final overall survival analysis showed comparable survival with trabectedin or dacarbazine, patients with advanced leiomyosarcoma or liposarcoma achieved clinically meaningful and statistically significant improvement in progression-free survival with trabectedin. Furthermore, the overall survival may have been confounded by use of post-study therapies that were delivered earlier in the dacarbazine arm. In October, 2015, the US Food and Drug Administration approved trabectedin for the treatment of unresectable or metastatic liposarcoma and leiomyosarcoma.

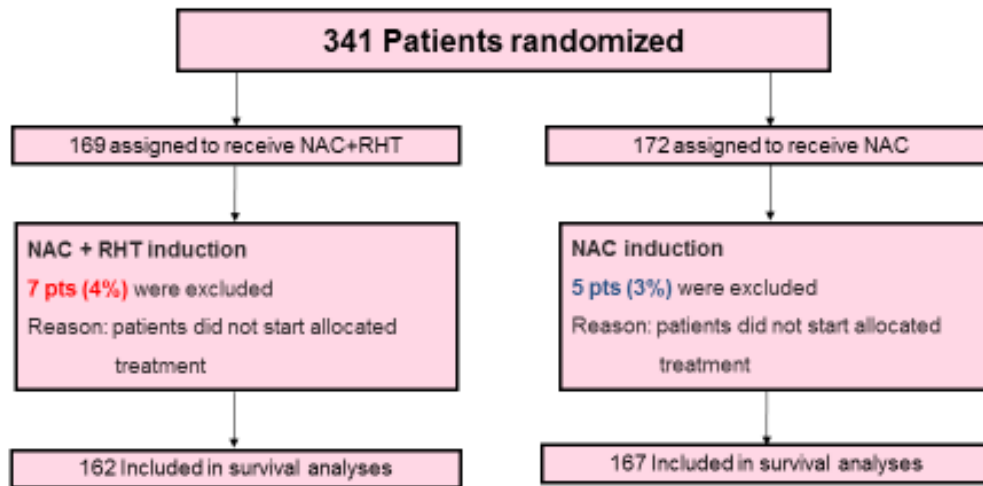
### Long-term results show overall survival more than doubled with the addition of regional hyperthermia to neoadjuvant chemotherapy in patients with localised high-risk soft tissue sarcoma

Lead investigator Rolf Issels, München-Großhadern Klinikum Grosshadern, Munich, Germany reported findings of an analysis after long term follow-up of a phase III study showing that regional hyperthermia as an induction treatment added to neoadjuvant chemotherapy enhanced clinical benefit across all measured parameters in patients with localised high-risk soft tissue sarcoma. The randomised, multicentre, phase III EORTC trial of sole neoadjuvant chemotherapy or in combination with regional hyperthermia enrolled patients with localised high-risk soft tissue sarcoma of 5 cm or larger that were FNCLCC grade 2 or 3, that were stratified by site, disease

presentation, and centre, then randomised to receive etoposide 125 mg/m<sup>2</sup>, ifosfamide 1500 mg/m<sup>2</sup> plus adriamycin at 50 mg/m<sup>2</sup> for 4 cycles or the same regimen plus regional hyperthermia at 42°C for 60 min on days 1 and 4 as induction therapy. Baseline and disease characteristics, including concomitant local surgical and/or radiotherapy interventions were well balanced between study arms. The primary endpoint of the study was locoregional progression-free survival (LPFS) and secondary endpoints included treatment safety, response, disease-free survival (DFS), and overall survival (OS).

The analysis done after a median follow-up of 74 months on the intent to treat population of 167 patients treated with neoadjuvant chemotherapy versus 162 patients treated with neoadjuvant chemotherapy plus regional hyperthermia showed LPFS rates of 40% versus 51%, and DFS of 34% versus 42%, respectively, HR 0.72; 95% CI 0.55, 0.94 (log rank p = 0.016). The OS analysis also favoured the adjunct hyperthermia arm: Median OS was 15.4 years for patients receiving regional hyperthermia versus 6.2 years for patients receiving only neoadjuvant chemotherapy. At the 5-year follow-up, the OS rate was 63% (95% CI 55%, 70%) versus 51% (95% CI 43%, 59%) in the respective arms and OS was significantly prolonged with regional hyperthermia compared with sole chemotherapy, HR 0.74; 95% CI 0.55, 0.99 (log rank p = 0.047).

## Study Flow



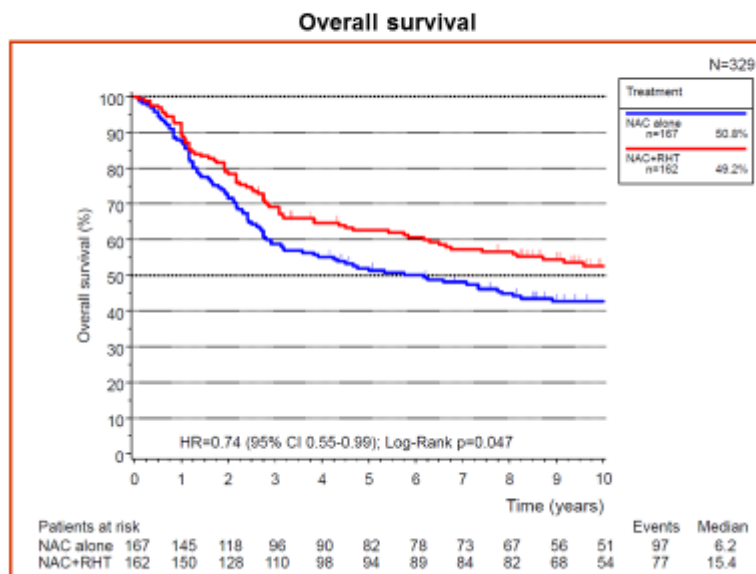
The median follow-up of 329 pts was 74 months (155 censored: 132 months)  
Last date of follow-up: 12/2014

**Caption:** EORTC 62961/ESHO – Study flow

**Credit:** Rolf Issels

By December 2014, 221 (67%) patients overall had relapsed and 174 (53%) had died. After 9 years of follow-up, OS rates of 54% (95% CI 46%, 62%) compared to 43% (95% CI 35%, 50%) were demonstrated in the hyperthermia arm compared to the adjuvant chemotherapy arm, respectively. LPFS also was significantly higher in the hyperthermia arm compared to the adjuvant chemotherapy arm; HR 0.71; 95% CI 0.54, 0.93 (log rank  $p = 0.012$ ). The toxicity profile was consistent with prior experience of neoadjuvant chemotherapy and hyperthermia; no unexpected or new safety findings were reported. The authors suggest that the beneficial effects on survival might be linked to the known heat shock related immune effects induced by hyperthermia. EORTC 62961/ESHO, NCT00003052. Issels *et al.* Abstract 13LBA.

## Results of phase 3 study (n=329 pts)



**Caption:** EORTC 62961/ESHO – Overall survival

**Credit:** Rolf Issels

### Practice point and future research opportunities

This was a positive trial that met the primary endpoint, locoregional progression-free survival, and demonstrated significantly improved overall survival, in a high-risk population. While confirmation is warranted, these findings support adding regional hyperthermia to standard neoadjuvant chemotherapy in patients with localised high-risk soft tissue sarcoma.

### A French nationwide survey shows improved key parameters after incorporating two expert networks for desmoid tumour management

Nicolas Penel, Oscar Lambret Centre, Lille, France, presented findings showing that the founding of 2 expert networks for desmoid tumour improved the diagnosis and management modalities of a very rare tumour at a national level. He described how the French National Cancer Institute and Patient advocacy Groupe (SOS Desmoide) had supported the labeling of 2 expert networks in 2009: one was the RRePS, which comprised a network of expert pathologists to systematically

confirm every suspected case of desmoid tumour, and NetSarc, a network gathering centre with expertise in adult sarcoma and desmoid tumour management. This study analysed the diagnosis modalities from 903 successive cases from 2010 to 2013 to evaluate the activities of both networks by prospectively collecting data using a nationwide database.

Out of a total of 903 patients identified during this interval, 846 were aged  $\geq 18$  years and were eligible for management by NetSarc. Of these, 414 (48.9%) patients were treated by the NetSarc organisation; this rate of patients managed within the network has constantly increased since 2010, from 36.95% to 50.0%. Furthermore, the median time to management by NetSarc centres has decreased from 440 to 67 days ( $p < 0.0005$ ). The predictive factors associated with management by NetSarc centres that emerged were being female, 50.0% women compared with 41.2% men ( $p = 0.0016$ ), and having a soft tissue rather than visceral desmoid tumour (50.8% versus 37.6%;  $p = 0.02$ ). Patients treated within NetSarc were also younger at mean 44 versus 48 years ( $p = 0.005$ ). However, the analysis revealed that management within NetSarc was not related to tumour size or beta-catenin mutational status.

This analysis also revealed that key-indicators of the RRePS constantly improved from 2010 to 2013, as reflected in the number of confirmed cases, which rose from 173 to 273, and the rate of cases diagnosed with microbiopsies, which rose from 30.6% to 40.7%. Additionally, the rate of analysis done on the beta-catenin mutational status increased from 87.8% to 94.0%. Another key indicator, the mean delay for pathological diagnosis confirmation from the date of first biopsy/surgery was seen to consistently decrease over this time from 107 to 47 days. The authors plan a prospective analysis of the impact of these networks upon patient outcome. Penel *et al.* Abstract 3400.

### Practice point and future research opportunities

Management of rare tumours, including diagnosis confirmation and prompt management in referral centers remains a public health challenge; however this survey demonstrates how both expert networks improved the overall confirmation of cases, and other indicators, such as time to pathological diagnosis.

## SUPPORTIVE CARE AND PALLIATION

### A sub-analysis of the NEXT study shows biosimilar filgrastim is safe and controls development of febrile neutropenia in patients with lung cancer undergoing cytotoxic chemotherapy

Didier Kamioner, Hopital Prive de l'Ouest Parisien, Paris, France presented findings from a sub-analysis of data from patients with lung cancer participating in the NEXT Trial, which was conducted in multiple centres throughout France as a prospective, non-interventional, longitudinal study to assess the incidence of febrile neutropenia and infection as well as safety following treatment with biosimilar filgrastim. Patients were evaluated upon study inclusion, during treatment and after chemotherapy. NEXT enrolled 2114 patients who were treated with chemotherapy for malignancies other than chronic myeloproliferative and myelodysplastic syndrome and also received Nivestim™, a biosimilar filgrastim. Of these, data from 293 patients with lung cancer receiving 1 to 6 cycles of chemotherapy and biosimilar filgrastim were included in the sub-analyses; biosimilar filgrastim was administered as prophylaxis in 98.3% of these patients (primary prophylaxis in 93.1% of patients) and as curative treatment in 1.7% of patients. In this subgroup, 74.7% of patients were male, 28.7% had stage M0 lung tumours, and metastases were identified in 69.1% of patients.

Febrile neutropenia was reported as an adverse event (AE) in 2.9% of patients receiving biosimilar filgrastim as primary prophylaxis and in 10.5% of patients receiving it as secondary prophylaxis. Infection occurred in 3.0% of patients overall receiving biosimilar filgrastim as prophylaxis. Chemotherapy cycles were delayed due to febrile neutropenia in 6.9% and chemotherapy dose reductions were required in 7.3% of prophylactic patients. Hospitalisation was needed for 3.4% of prophylactic patients due to febrile neutropenia or infection for an average of 10.5 days. Overall, 14.6% of prophylactic patients were associated with a high risk of developing febrile neutropenia; 44.6% had intermediate risk and 40.7% of patients were at low risk of developing febrile neutropenia (2010 NCCN guidelines). AEs other than infection or febrile neutropenia were reported in 15.3% of all patients; the most commonly reported AEs that occurred in >2% of patients were muscle and/or bone pain, nausea, headache and other. Kamioner et al. Abstract 1501.

#### Practice point and future research opportunities

Biosimilar filgrastim (Nivestim™) is a granulocyte-colony stimulating factor (G-CSF) approved for the treatment of infection and febrile neutropenia, which is a frequent and potentially serious complication of chemotherapy. In this subgroup analysis of patients with lung cancer receiving chemotherapy, biosimilar filgrastim was well tolerated and effective in preventing febrile neutropenia and infection, and provided the majority of these patients with intermediate or low risk of developing febrile neutropenia.

## Visualization and relaxation as anxiety reducing techniques in breast and prostate cancer patients undergoing chemotherapy: Findings from a randomised controlled trial

Andreas Charalambous, Cyprus University of Technology, Nursing Department-School of Health Sciences, Limassol, Cyprus discussed a form of care that can ameliorate the anxiety and depression caused by cancer diagnoses and treatment that is reflected by the high prevalence rate of depression and anxiety in cancer patients, which is estimated to range between 55 to 65%. Prolonged distressed emotional states may lead to additional somatic problems or induce behavioral changes that can have further debilitating effects on the patients' psychological well-being and overall quality of life.

In this randomised controlled trial, 212 patients with breast or prostate cancer undergoing chemotherapy were randomly assigned 1:1 to either the control group, to receive standard care, or to the intervention group, which included relaxation and visualization techniques. Patients were observed for 3 weeks and assessed with the SAS and BECK-II questionnaires for anxiety and depression, respectively. In addition, cortisol and saliva amylase levels were measured in patient saliva samples.

The 106 patients in the intervention group showed significantly lower anxiety change scores and depression change scores of  $-6.3 \pm 6.1$  and  $-17.7 \pm 7.3$ , respectively, than 106 patients in the control group, where score changes were  $4.9 \pm 5.9$  and  $11.7 \pm 8.5$ , respectively ( $p < 0.00001$ ). Baseline cortisol levels in the intervention group were  $0.30 \pm 0.25$ , were seen to gradually decrease up to week 3 to  $0.16 \pm 0.18$ , whereas baseline cortisol levels in the control group levels were  $0.21 \pm 0.22$  and were seen to double by week 3 to  $0.44 \pm 0.35$ . Similar results were reported for amylase levels ( $p < 0.0001$ ). NCT01275872. Charalambous *et al.* Abstract 1502.

### Practice point and future research opportunities



Although the mechanisms by which cognitive behavioral interventions can modify or interfere with the stress response to external stimuli remain unknown, these trial findings show that relaxation and visualization techniques more effectively manage patients' anxiety and depression than standard treatment alone in patients diagnosed with breast or prostate cancer receiving chemotherapy.

## Improved emesis control with adjunct fosaprepitant in women receiving pelvic radiotherapy plus cisplatin for cervical cancer

Christina H Ruhlmann, Odense University Hospital, Odense, Denmark presented findings from the first study to address emesis control, a cornerstone of palliative care, in women receiving pelvic radiotherapy. In the GAND-emesis trial, fosaprepitant, a neurokinin-1 receptor antagonist, was added to an anti-emetic regimen and demonstrated significantly improved emesis control in women being treated with radiotherapy and cisplatin for cervical cancer, where treatment-related vomiting accounts for a majority of adverse events and study discontinuation. Emesis control has been most often investigated in chemotherapy trials, although nausea and vomiting are known to be a major adverse effect of delivering radiotherapy to the abdominal area; moreover, neurokinin-1 receptor antagonists had not previously been evaluated for efficacy with radiation.

This was an investigator initiated multinational randomised double-blind placebo-controlled phase III trial that enrolled 246 chemotherapy and radiotherapy naive women with cervical cancer from 4 European centres. Patients with scheduled brachytherapy prior to the radiation fraction or with the diagnosis of another other concurrent malignancy were excluded from the study, as were patients experiencing emesis or moderate to severe nausea within the 24 hours preceding the first dose of study medication. All patients received a regimen of 5 fractions per week of radiotherapy at 2 Gy to the pelvis (median Gy 50 external beam radiation therapy dose), plus anti-emetic prophylaxis with intravenous palonosetron plus oral dexamethasone prior to the administration of cisplatin at 40 mg/mg<sup>2</sup> given on day one weekly for 5 weeks. Both cohorts also received dexamethasone twice daily on days 2, 3, and 4 of each cycle, which was repeated for 5 weeks. Patients were allowed anti-emetic rescue medication. The patients were randomised to receive either 150 mg i.v. fosaprepitant daily or placebo in addition to this regimen and daily patient diaries were maintained. The primary endpoint was the no emesis rate sustained over days 1 through 35, and secondary endpoints were complete response (CR), nausea, and safety. Efficacy assessments were made daily and safety assessments were made weekly. In all, 234 patients, 118 in the fosaprepitant arm

and 116 in the control arm, received study medication and were eligible for the efficacy evaluation. Patient baseline characteristics were well matched between groups.

Patients receiving fosaprepitant plus anti-emetics demonstrated a statistically significant higher sustained no emesis rate of 76.7% compared to 65.1% in patients receiving standard anti-emetics; 95% CI 0.38, 0.99 ( $p = 0.048$ ). The cumulative incidence over the course of the trial was lower with fosaprepitant, with patients experiencing 17% less emesis on average: During weeks 1, 2, 3, 4, and 5 no emesis was sustained by 86%, 78%, 73%, 69% and 66% of patients receiving fosaprepitant compared with 78%, 66%, 59%, 53% and 49% of patients receiving anti-emetics only ( $p = 0.008$ ). At 168 hours (cycle one end) the rates of no nausea were 42% with fosaprepitant compared to 25% with placebo ( $p = 0.005$ ). CR, defined as no emesis and no use of rescue anti-emetics within 24 hours post initiation of therapy, was achieved by 92% of fosaprepitant patients versus 86% of placebo. CR at 120 and 168 hours post therapy was 74% and 71% versus 64% and 59% in the respective cohorts. CR over days 1 to 35 was achieved by 51% of fosaprepitant patients versus 33% of placebo patients ( $p = 0.005$ ) and no nausea was sustained over the same duration by 14% versus 8% of fosaprepitant and placebo patients, respectively ( $p = 0.009$ ).

The adverse events (AE) profile of both cohorts was similar: The most commonly reported (affecting 10 or more patients) AEs were loss of appetite, fatigue, headache, dizziness, hearing impairment, tinnitus and nervous system disorders. NCT 01074697. Ruhlmann et al. Abstract 34LBA.

### Practice point and future research opportunities

This study is to be congratulated for addressing the issue of nausea and vomiting involving radiation delivered to the abdomen, since most studies on emesis control are done with chemotherapy. Adding fosaprepitant to palonosetron and dexamethasone provided significantly better emesis and nausea control over palonosetron and dexamethasone alone in women receiving chemoradiation for cervical cancer; the findings were both statistically and clinically significant.

**Supersaturated calcium-phosphate rinse better than sodium chloride in oral complaints in patients receiving TKI or mTOR inhibitor treatment for various cancers**

Christine Boers-Doets, Leiden University Medical Centre, Leiden, The Netherlands, headed a team that evaluated the utility of a supersaturated calcium-phosphate mouth rinse, SCPR/Caphosol<sup>®</sup>, in decreasing oral complaints, including aphthous ulcerations, oral pain, taste change, difficulty swallowing, difficult oral intake, burning sensation and dry mouth, compared with NaCl (0.9%) in cancer patients being treated with tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors. The double-blind phase III randomised cross-over study enrolled 60 patients experiencing oral complaints while being treated with either a TKI or mTORi. During the first rinse period comprising 14 days, 20 patients received SCPR and 39 patients received NaCl. For the second 14 day period, the patients were switched to the opposite treatment arm; 10 of 20 SCPR patients were given NaCl and 27 of 39 NaCl patients received SCPR. The patient-reported oral complaints were evaluated 3 times weekly by the change in the Vanderbilt Head and Neck Symptom Survey 2.0 (VHNSS) scores, using a 10-point scale.

Of the enrolled patients, 19 were receiving everolimus, 16 sunitinib, 14 pazopanib, 10 sorafenib and one was on temsirolimus. Treatment was for metastatic renal cell carcinoma in 24 patients, metastatic breast cancer in 11, gastrointestinal stromal tumours in 6, hepatocellular carcinoma in 5, and 13 patients had other diagnoses. One patient was inevaluable.

The median VHNSS score consisting of 48 items regarding oral complaints was 0.88 (range: 0 to 5.51) for all patients. This score was significantly lower in the SCPR arms at median 0.74 (range: 0 to 4.85) compared to median 1.04 (range: 0 to 5.51) in the NaCl arms ( $p = 0.023$ ). Mixed model ANOVA showed a 50% reduction ( $p = 0.1$ ) of total median VHNSS score (1.64 to 0.81) in the NaCl arm during the first period. Before cross-over, the VHNSS scores decreased significantly for the NaCl arm over time ( $p = 0.001$ ), whereas these scores showed a decrease or borderline significance ( $p = 0.085$ ) for the SCPR arm, which may have been affected by the small sample size of patients starting with SCPR rinse. The effect of the SCPR rinse was more prominent in the larger group of patients beginning with NaCl rinse in the first period of study treatment.

The greatest effect with SCPR was noted in the subgroups of patients with dry mouth and burning sensation. For dry mouth, the SCPR median score was 0.31 (range: 0 to 6.25) versus median 0.50 (range 0 to 7.63) with NaCl ( $p = 0.004$ ) and for burning sensation, SCPR patients reported median scores of 0.75 (range: 0 to 10) versus a median score of 1.25 (range 0 to 8.50) with NaCl ( $p = 0.017$ ). Boers-Doets *et al.* Abstract 35LBA.

### Practice point and future research opportunities

Supersaturated calcium-phosphate rinse shows promise for minimising oral complaints associated with treatment for cancer with TKIs and mTORis, especially dry mouth and oral burning sensation. Reducing treatment side effects is an important aspect of medical treatment of cancer.

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