ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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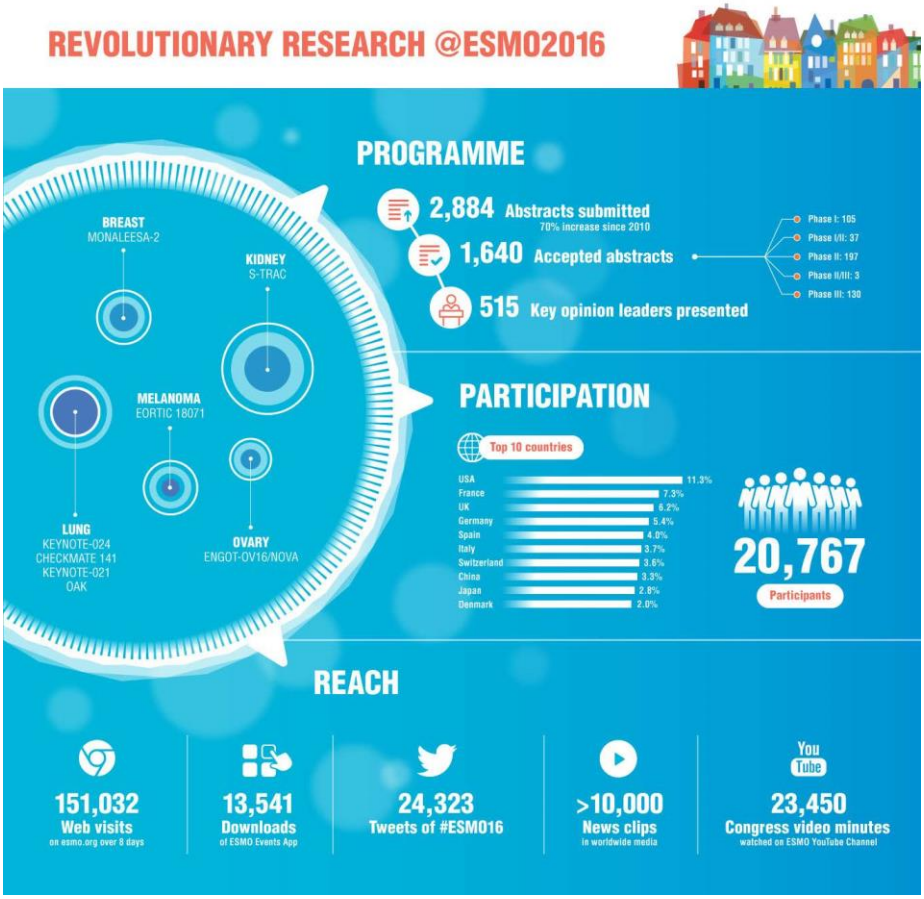
Summary

The European Society for Medical Oncology (ESMO) 2016 Congress, held October 7 to 11 in Copenhagen, Denmark, was a record-breaker on all levels. It was resounding success and in a dedicated infographic you can find the congress programme statistics. A primary emphasis in the scientific programme was placed on two areas: precision medicine and immunology and immunotherapy across multiple tumour types and how these advances change the treatment landscape in oncology. This report is an overview of key scientific presentations made during the Congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2016 scientific programme, as well as advances in oncology.



ESMO 2016 record breaking Congress

INTRODUCTION

The 2016 Congress of the European Society for Medical Oncology (ESMO) was held in Copenhagen, Denmark from 7 to 11 October. The Congress broke all records from the preceding years, with a 28% increase in attendance, 30% more abstract submissions and record breaking number of simoultaneous publication of full results in top scientific medical journals. There was a lso a substantial rise in social media activities. The ESMO Congress App was downloaded significantly more than in last years. The participants came from 124 countries worldwide. The majority (62%) of the 20,767 delegates were medical oncologists and the remainder included clinical oncologists, radiologists, pathologists, surgical, and haemato-oncologists, as well as professionals from over 20 other fields. Primarily, the delegates worked in hospitals, with 32.2% affiliated with university hospitals, 23.8% in general hospitals with teaching functions, and 11.5% of delegates affiliated with general hospitals without teaching functions. The pharmaceutical industry was represented by 8.7% of delegates. In total, 6.5% of delegates were affiliated with a comprehensive cancer centre. Also represented were non-profit research, biotech, and academic institutions, as well as private out-patient facilities.

In addition to a broad and up-to-date educational programme, the intensive scientific programme covered all fields of oncology, and included new research that was represented by the 1640 abstracts that were chosen for presentation out of the 2884 abstracts that were submitted. Of the accepted abstracts, 130 involved clinically relevant, potentially practice-changing phase III trials. The most (503) abstracts involved gastrointestinal tumours, while 375 abstracts dealt with basic science and translational research. Breast cancer was covered in 327 abstracts, 284 abstracts discussed genitourinary tumours, followed closely by 276 abstracts on chest tumours. More than 100 abstracts represented each of the fields of supportive and palliative care, gynaecological cancers, public health and health economics, and head and neck cancer, whereas 101 abstracts covered the burgeoning immunotherapy of cancer topic. Cancer types including melanoma, haematological malignancies, CNS tumours, sarcoma, neuroendocrine and endocrine tumours were all represented plus a miscellaneous category, which comprised also rare cancers. The crucial need for new treatment options was actively addressed in 78 abstracts involving developmental therapeutics.

Leaders in all fields of oncology participated as enthusiastic speakers, as thought provoking invited discussants or as well-informed session chairs in hundreds of diverse scientific sessions. Educational sessions, symposia, industry satellite seminars, and debates rounded out the diverse programme.

A brief summary of some of the scientific findings presented during the ESMO 2016 Congress follows.

BASIC SCIENCE

EPHA2 as a potential marker of resistance to anti-EGFR agents in metastatic colorectal cancer

Giulia Martini, Department of Oncology, AOU Seconda Università degli Studi di Napoli in Naples, Italy and colleagues studied the possible role of the tyrosine kinase inhibitor, EPHA2, as a potential marker of resistance to anti-EGFR drugs in colorectal cancer (CRC). The effect of the EPHA2 inhibitor ALW-II-41-27 with and without cetuximab on cell survival and drug sensitivity was evaluated by the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay, which measures mitochondrial activity, and by western blot analysis using a panel of CRC cell lines. Cell lines sensitive to anti-EGFR agents included GEO and SW48 cells, and resistant lines included HCT116, SW620, LOVO, SW480, HCT15, and GEO-CR plus SW48-CR, which also demonstrates acquired cetuximab resistance. Flow cytometry was used to analyse apoptosis and for cell cycle analysis, and SW48-CR subcutaneous xenograft models were used for in vivo experiments. EPHA2 expression was assessed by immunohistochemistry (IHC) in metastatic CRC tumours.

Using these methods, the investigators found that EPHA2 was differentially activated among cell lines with high levels of phosphorylation, including HCT116, SW620, LOVO, GEO-CR and SW48-CR cells. The sensitivity of CRC cell lines to ALW-II-41-27, expressed as IC_{50}, differed among the lines studied, and ranged from 0.05 to 2 mM; the most sensitive cell lines were HCT116, SW620, LOVO, SW48-CR, HCT15, and GEO; GEO-CR and SW48 showed the highest resistance to ALW-II-41-27.

To address whether EPHA2 inhibition could overcome primary and acquired resistance to cetuximab, a combination of ALW-II-41-27 plus cetuximab was tested in resistant cell lines. The combination induced synergistic anti-proliferative and apoptotic effects in HCT15 cells with primary, and in GEO-CR and SW48-CR cells, which have acquired resistance to cetuximab. The synergistic activity of the combination was confirmed by a reduction of pEPHA2 levels and a marked inhibition of activated pMAPK and pAKT. Cell cycle analysis showed the combination induced greater G2 phase arrest compared with sole ALW II-41-27. A detailed evaluation of EPHA2 expression by IHC in tumours from patients with mCRC receiving anti-EGFR therapy was presented and the in vivo experiment in SW48-CR subcutaneous xenograft models is ongoing. Martini *et al.* Abstract 1O

Practice point and future research opportunities

Both primary and acquired resistance to anti-EGFR therapy was overcome in vitro by ALW-II-41-27, a selective EPHA2 inhibitor. These results suggest that EPHA2 may be potential therapeutic target, and pEPHA levels may be a putative biomarker in mCRC treatment.

BIOMARKERS

Large-scale evaluation of tumour mutational burden and microsatellite instability status

Garrett M. Frampton, Research and Development, Foundation Medicine, Cambridge, USA, and collaborators used comprehensive genomic profiling (CGP) targeting greater than 500x sequencing coverage (non-PCR duplicate reads) to capture the full coding regions of 315 genes. The investigators performed CGP on more than 40,000 cancer specimens from individual patients, representing over 400 unique sub-types of cancer to determine the contribution made by microsatellite instability (MSI) to the overall tumour mutational burden (TMB). MSI and TMB were each then assessed as biomarkers of response to immunotherapy in a large cohort of patients with advanced cancer representing a broad array of tumour types. MSI status was determined by assessing the indel alterations occurring at 114 microsatellites covered by the CGP test. TMB was determined by evaluating the number of somatic, coding, base substitution, and indel mutations occurring per megabase of coding genome targeted on the test. Tumours with ≥ 20 mutations per megabase were considered to have high TMB.

The investigators found that 1.4% of cases were MSI-High, while 7.1% of cases had high TMB. High TMB was observed in 85% of MSI-High cases; interestingly, the converse was not observed, with numerous cases with high TMB being observed that did not show evidence of MSI.

The results were highly disease specific with some tumour types, notably lung, skin, and urinary cancers, that were MSI-High but with very few (<5%) high TMB cases. In gastrointestinal, ovarian, and endometrial cancers more than 75% of high TMB cases were also MSI-High. A meaningful fraction of cases with high TMB and no evidence of MSI was observed in all tumour types. The full landscape of TMB and MSI across 40,000 cases and hundreds of cancer sub-types was presented at the conference. Frampton *et al.* Abstract 52O

Practice point and future research opportunities

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

Multidisciplinary molecular tumour board enables selection accrual for clinical trials and targeted therapy in cancer patients

Christian D. Rolfo, Early Clinical Trials Unit & Center for Oncological Research of Antwerp (CORE), Antwerp University Hospital in Edegem, Belgium, noted that using Next-Generation Sequencing (NGS) and other molecular profiling techniques to identify druggable targets has

changed clinical practice in oncology. To facilitate these gains, the Molecular Tumour Board (MTB) has become a crucial multidisciplinary tool for results interpretation and implementation of treatment, including the inclusion of patients in clinical trials. Professor Rolfo and colleagues conducted a retrospective analysis of a cohort of patients with several advanced solid tumours that were not candidates for standard treatment that had been included in the MTB, which is a consultation for the phase I – Early Clinical Trials Unit of the Antwerp University Hospital. The patients all had a molecular profile (MP) that was discussed in the MTB and this analysis included patients with MTBs done in house and also by commercial NGS platforms. A subgroup of these patients also had samples for immunochemistry (IHC) and/or in situ hybridization (ISH) analysis.

This study included 133 national and international patients who provided 141 tissue samples. The median patient age was 59 years old (range: 18 to 85), and 56% of patients were female. Genomic alterations were detected in 107 (75.9%) samples at an average of 3.44 alterations; 86 (80.4%) of these alterations corresponded to gene mutations in the NGS panel. Approximately 50 (58.1%) samples harboured more than one mutated gene.

The most frequently mutated genes in this cohort were TP53 at 32%, KRAS at 13%, PIK3CA at 8%, and 7% of the alterations were in the APC gene. In the subgroup analysis of patients with additional MP information (IHC=X: CISH=4: FISH=6) the more common alterations were 9% each in TOPO1 and TOP2A, and 8% in both MGMT and PTEN. The primary tumour sites most frequently implicated were lung in 14.9% of samples, colon in 12.1%, pancreas in 9.2%, and breast in 7.8% cases. The MTB recommended treatment in 78 (55%) of the cases, including matched therapy in 55 (70.5%) of cases, and non-matched therapy in 23 (29.5%) cases. Based on MP information 29 (37%) patients were included in clinical trials, and 5 (6.4%) patients received compassionate use. Rolfo *et al.* Abstract 54PD

Practice point and future research opportunities

The multidisciplinary molecular tumour board review enabled a majority of patients with advanced cancer to be offered targeted therapy or entry into clinical trials based on molecular profiling. Access to suitable target drugs and clinical trials are crucial to guarantee that cancer treatment moves forward at the same rate as scientific discovery. National programmes for reimbursement would facilitate these efforts.

Dabrafenib shows anti-tumour activity in paediatric patients with BRAF V600–mutant relapsed or refractory low-grade gliomas

Principle investigator Mark Kieran of the Paediatric Medical Neuro-Oncology Department of Dana-Farber Cancer Institute and Boston Children's Hospital pointed out that BRAF V600 mutations are present in approximately 15%-20% of patients with paediatric low-grade gliomas who are known to have poorer survival and lower objective response rates than paediatric patients with gliomas and wild-type BRAF. Dr. Kieran and colleagues conducted the first study

to evaluate dabrafenib, which inhibits the V600-mutant form of the BRAF kinase, in 32 paediatric patients aged 2 to 17 years with BRAF V600-mutant relapsed or refractory disease. The phase I dose-finding part of the study comprised 15 patients and tested 4 dose levels up to, and including, the recommended phase II (RP2) dose of 4.5 mg/kg/day in patients aged 12 or older; patients younger than 12 received 5.25 mg/kg/day of dabrafenib divided into two equal daily doses. Overall 24 patients, including 17 patients in the phase II part of the study, received the RP2 dose of dabrafenib.

At data cut-off, 22 patients remained on study. The independently confirmed overall response rate (ORR), by Response Assessment in Neuro-Oncology (RANO) criteria, was 41% (95% confidence interval [CI] 24%, 59%), and consisted of 2 complete responses (CRs) and 11 partial responses (PRs). The median duration of response was 11 months and 8 responders had an ongoing response. An additional 13 (41%) patients had stable disease lasting 6 months or more, of whom 11 showed an ongoing response. The confirmed ORR per investigator assessment was 72% (95% CI 53, 86), which included one complete response (CR) and 2 partial responses (PRs).

The paediatric patients showed adverse events (AEs) with dabrafenib that were similar to adults, and included frequent low-grade pyrexia, vomiting, fatigue, headache, and rash. The most frequent grade 3/4 AE was pneumonia. No cases of cutaneous squamous cell carcinoma occurred. One patient discontinued the study due to a significant allergic reaction following the initial dosing and again upon re-challenge. The investigators are planning to give dabrafenib together with the MEK inhibitor trametinib in a future trial, since the combination has shown a longer duration of progression-free survival than either drug used alone in adults. EudraCT Number: 2012-001499-12. Kieran *et al.* Abstract LBA19_PR

Practice point and future research opportunities

Although paediatric low-grade glioma generally carries a good prognosis, the 15% to 20% of children with BRAF V600 mutation fare less well. There is a need for improved treatment options for these patients who often have lifelong cognitive damage and secondary malignancies due to radiation therapy. There is a paucity of randomised data for treatment of brain tumours in children since the tumours are rare and the trials are difficult for ethical reasons. The promising results seen with targeted therapy in this study are limited by the small population and short follow-up. These findings will have implications for clinical practice, however, longer follow-up is needed to find out how long the responses last and whether there is any long-term toxicity.

Vemurafenib is active in diverse BRAF V600-mutated tumour types but not in tumours without V600 mutation

Patients with BRAF non-V600 mutated tumours showed no benefit from vemurafenib, according to Jean-Yves Blay, Medical Oncology, Centre Léon Bérard, in Lyon, France. Professor Blay presented results from the second ACSE vemurafenib study, which is part of a programme undertaken by the French National Cancer Institute to allow patients to have safe and controlled access to targeted therapies outside of the labelled indication. More than 1500 patients were

screened for mutations at 96 centres throughout France, which yielded 78 patients with tumours harbouring BRAF V600 and BRAF non-V600 mutations. These patients were enrolled in this phase II study, which comprised 2 cohorts: The dedicated treatment cohort contained patients with diverse BRAF V600 mutation positive cancers including lung, ovarian, bladder, thyroid, prostate cancers, cholangiocarcinoma, sarcoma/gastrointestinal stromal tumour (GIST), multiple myeloma, chronic lymphocytic leukaemia (CLL), and HCL, and the specific miscellaneous cohort containing 6 patients with BRAF V600 mutation, and 14 patients with non-V600 BRAF (exon 11, 15) mutated tumours, or other BRAF alterations.

All patients were treated with vemurafenib at 960 mg twice daily. The median age of the patients was 67 (range: 18 to 84) years and 51% of patients were female. The efficacy endpoint was objective response rate (ORR), which was evaluated every 8 weeks by RECIST v1.1 criteria for solid tumours and by specific criteria for myeloma, CLL and HCL. Data from 56 patients were analysed for response, which was reported by mutation status and cancer subtype.

The median duration of treatment was 1.9 months (range: 0.2 to 11.0 months). In the dedicated cohort of patients with BRAF V600 positive cancers, 31 patients with NSCLC demonstrated an ORR of 43%; 13 patients achieved partial response (PR), 6 showed stable disease (SD), 7 patients experienced progressive disease (PD), 4 patients died, and the data were missing for one patient. In patients with HCL, 4 of 4 patients having evaluable data showed an ORR of 100%; 2 patients demonstrated PR and 2 patients had SD. The one patient with sarcoma died. Of the 2 patients with cholangiocarcinoma, one patient also died and one patient demonstrated SD. Of the 3 patients with thyroid cancer, one patient demonstrated SD and 2 patients had PD.

In the miscellaneous cohort, 5 of 6 patients with BRAF V-600 mutations had evaluable data: PR was achieved by 3 of these patients and 2 patients showed SD, resulting in an ORR of 60%. All 6 patients with BRAF non V-600 mutated tumours experienced PD. The most frequently reported treatment-related adverse events of grade 3 or greater were skin and gastrointestinal toxicities. Blay *et al.* Abstract 55PD

Practice point and future research opportunities

Nationwide screening for patients with BRAF mutation enabled rapid access to vemurafenib treatment in this trial. Vemurafenib is approved for BRAF mutated melanoma and has shown activity in other non-melanoma tumours that harbour BRAF-V600E-mutations. Findings from a phase II trial of vemurafenib in previously treated patients with advanced disease and BRAF mutated tumours indicate the drug is effective in patients with diverse BRAF V600-mutated tumours, which have been reported to be present at low (<5%) frequency. These reports were confirmed by results from this trial where important antitumour activity was seen with vemurafenib in NSCLC, HCL, and miscellaneous V600 mutated tumours, but not in patients with BRAF non-V600 mutations.

BREAST CANCER - Early Stage Breast Cancer

Large data analysis reveals similar survival outcomes with sequential or concomitant administration of adjuvant trastuzumab in HER2-positive breast cancer

Xavier Pivot, Oncology, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, and a team of investigators evaluated sequential versus concomitant administration of adjuvant trastuzumab using combined data of 11,728 patients with breast cancer that participated in the PHARE and SIGNAL trials. PHARE was a randomised phase III clinical trial (NCT00381901) and SIGNAL (RECF1098) was a prospective trial that was designed to include genome wide association study (GWAS).

In the SIGNAL/PHARE cohort nearly half, 5,502, breast cancer cases involved HER2-positive tumours.

Sequential administration of taxane-based chemotherapy and trastuzumab was delivered to 1897 (34.5%) patients, and 3605 (65.5%) patients received concomitant administration of taxane-based chemotherapy plus trastuzumab. Overall survival (OS) and disease-free survival (DFS) estimates made using the Kaplan-Meier method where similar regardless of the mode of administration; for the OS comparison (hazard ratio [HR] 1.01; 95% confidence interval [CI] 0.86, 1.19) and for the DFS comparison (HR 1.08; 95%CI 0.96, 1.21). Pivot *et al.* Abstract 144O

Practice point and future research opportunities

Several clinical trials in early HER2 positive breast cancer have assessed either sequential or concomitant incorporation of trastuzumab plus chemotherapy; however, only the NCCTG-N9831 trial prospectively compared the two modalities and showed no statistically significant difference between methods. The results from this analysis of data from the prospective SIGNAL and PHARE trials suggest that the sequential administration of trastuzumab given after the completion of adjuvant chemotherapy may provide similar benefit as concomitant administration of trastuzumab and taxane chemotherapy in the adjuvant setting.

Derived neutrophil-to-lymphocyte ratio proposed as a prognostic biomarker in early breast cancer

Alberto Ocaña Fernandez, Research Unit and Medical Oncology, Albacete University Hospital, Albacete, Spain, and colleagues investigated the utility of a marker of inflammation, derived neutrophil-to-lymphocyte ratio (dNLR), as a putative prognostic marker in subgroups of women with early breast cancer.

The investigators conducted a retrospective analysis of women with early breast cancer with axillary involvement participating in the randomised, phase III GEICAM/9906 trial of adjuvant fluorouracil, epirubicin, and cyclophosphamide (FEC) compared to FEC/paclitaxel. The dNLR

was calculated as the ratio of neutrophils divided by the difference between total leukocytes and neutrophils measured in peripheral blood prior to treatment. The ratio was then evaluated as a potential marker of disease-free survival (DFS) and overall survival (OS), using Univariable Cox regression. Subgroups by PAM50 subtype and hormonal receptor expression were subsequently analysed, with the prognostic and predictive value of dNLR for DFS and OS as the trial's primary and secondary endpoints.

This analysis used data from 1243 patients who were enrolled from 65 Spanish sites and followed-up for a median of 10 years. The patient median age was 50 years (range: 23 to 76 years). Of the 66% of patients with available PAM50 subtype determination, 22% of the tumours were Luminal A, 21% Luminal B, 14% were HER2-enriched, 6% Basal-like, and 3% of tumours were Normal-like. The majority of tumours (47%) were oestrogen/progesterone receptor positive (ER-positive/PgR-positive) and 13% were receptor negative (ER-negative/PgR-negative) subtypes, according to immunohistochemistry (IHC).

The investigators determined the median dNLR was 1.35; interquartile range (IQR) 1.08 to 1.71. The dNLR greater than this median significantly associated with poorer DFS in patients with HER2-enriched tumours (per PAM50), hazard ratio (HR) 1.63; 95% confidence interval (CI) 1.04, 2.54 ($p = 0.03$). In patients with non-luminal (per PAM50) tumours, the dNLR greater than the median or a dNLR in a higher quartile were associated with poorer DFS ($p = 0.02$ and $p = 0.03$, respectively). A high dNLR grouped in quartiles associated with poorer DFS and OS in patients with ER-negative/PgR-negative tumours, as determined by IHC ($p < 0.001$ and $p = 0.007$, respectively). Ocaña Fernandez *et al.* Abstract 145O

Practice point and future research opportunities

In this study, the association of the dNLR to survival was evaluated per tumour subtype in early breast cancer. A higher than median dNLR was found to associate with poorer DFS in women with HER2-enriched and non-luminal intrinsic tumours identified by PAM 50; in addition, high dNLR also associated with worse DFS and OS in women with ER-negative/PgR-negative tumours, as determined by IHC. Further confirmatory study is necessary to determine whether higher than median dNLR may serve as a prognostic marker of survival in early breast cancer.

Large analysis reveals outcome and treatment disparities in elderly patients with hormone receptor positive breast cancer

Lead author Steven Shak, of Translational Sciences, Genomic Health, Inc., Redwood City, USA, provided findings from a study done using the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute to confirm an earlier finding that, not only are breast cancer diagnoses in older patients on the rise as life expectancy increases, but also older patients with hormone receptor (HR) positive breast cancer face a poorer prognosis (JAMA. 2012; 307:590). The investigators searched SEER registries that also contained 21 gene recurrence score (RS) results to evaluate breast cancer-specific mortality (BCSM), as previously

defined (JNCI. 2010;102:1584).

Data from 184,190 patients who were diagnosed from January 2004 to Dec 2011 with node negative (N0) HR-positive breast cancer, that did not have prior malignancy or multiple tumours were included in the study. Of these patients, 128,712 (70%) were younger than 70 and 55,478 (30%) were ≥70 years old. RS results were available for 35,487 (28%) patients aged less than 70 years; the median age of these patients was 55 years, 29% of patients had grade 1 disease and 54% were grade 2. Tumour size was ≤1 cm in 26% of patients and 54% of women had tumours >1-2 cm. In contrast, in the cohort of patients aged ≥70 years just 8% (4,647) of patients had RS results; the median age in this cohort was 73 years; 25% of patients had grade 1 and 55% of patients hade grade 2 disease. Tumour size was ≤1 cm in 20% of patients and >1-2 cm in 48% of patients.

Chemotherapy was used more often in younger than older patients; chemotherapy was used in 70% of patients overall but 72% of patients younger than 70 years received chemotherapy compared with 53% of patients ≥70 years ($p < 0.001$). In all patients, BCSM increased as recurrences increased; patients with RS < 18 had 5-year BCSM of 0.4%, compared to 1.4% in patients in the RS 18 to 30 group and 4.5 in patients with a RS of 31 or higher ($p < 0.001$).

As anticipated, the 5-year other-cause mortality was higher (11%) in patients ≥70 years compared with 4% in younger patients and was not associated with RS results ($p = 0.92$). Patients ≥70 years plus a RS ≥31 had the poorest BCSM of 11.7% ($p < 0.001$). Shak *et al.* Abstract 146O

Practice point and future research opportunities

The results of this large population-based observational study confirm that patients older than 70 years have a poorer prognosis than younger patients with node negative HR-positive breast cancer. The findings revealed that far fewer older patients received chemotherapy as treatment or recurrence score results were absent, contributing to breast cancer-specific mortality, which remains unacceptably high in US clinical practice for patients 70 years and older. Action is needed to address this disparity.

BREAST CANCER - Locally Advanced and Metastatic

Phase III results show first-line ribociclib and letrozole significantly improves PFS over letrozole monotherapy in HR-positive, HER2-negative, advanced breast cancer

Lead author Gabriel Hortobagyi from the University of Texas MD Anderson Cancer Center in Houston, USA presented the first preplanned interim analysis from the double-blind phase III MONALEESA2 trial that tested whether first-line ribociclib plus letrozole could improve progression-free survival (PFS) and delay or overcome the development of resistance to endocrine therapy in hormone receptor (HR) positive advanced breast cancer. MONALEESA2 enrolled 668 postmenopausal women who had not received prior systemic treatment for HR-positive, HER2-negative advanced breast cancer who were randomised to ribociclib at 600 mg/day, for 3 weeks on, one week off plus continuous letrozole at 2.5 mg/day, or to letrozole plus placebo.

The trial's primary objective, PFS, was met; patients in the ribociclib arm demonstrated a highly significant 44% improvement in PFS compared to the placebo arm, hazard ratio [HR] 0.556 (p = 0.00000329). At data cut-off, median PFS had not been reached with ribociclib versus 14.7 months in the placebo/letrozole arm. A significantly improved objective response rate of 53% with ribociclib plus letrozole was also seen compared to 37% with placebo/letrozole (p = 0.00028). The clinical benefit rate was 80% with ribociclib/letrozole compared with 72% with placebo/letrozole (p = 0.02). Overall survival data, a key secondary endpoint, were not yet mature.

The incidence of adverse events (AEs) was higher in the ribociclib arm; neutropenia occurred in 59% versus 1%, leukopenia 21% versus 1%, and lymphopenia occurred in 7% versus 1% of patients in the ribociclib/letrozole versus placebo/letrozolem respectively. A higher incidence of elevated alanine aminotransferase and elevated aspartate aminotransferase was also observed with ribociclib. Serious AEs occurred in less than 5% of patients in both arms. These results were published simultaneously online in *The New England Journal of Medicine (NEJM)*. NCT01958021. Hortobagyi *et al.* Abstract LBA1_PR; *NEJM* 2016; 375:1738-1748.

Practice point and future research opportunities

Endocrine therapy is an established first-line treatment for advanced breast cancer; however, resistance to endocrine therapy eventually develops in the majority of patients, leading to disease progression. CDK 4/6 inhibition with ribociclib is a valid treatment strategy to delay resistance development in for HR-positive advanced breast cancer. The interim results from the MONALEESA2 trial definitively demonstrate that adding ribociclib to letrozole therapy significantly improves PFS. These results represent a compelling proof of principle, and suggest a paradigm shift in metastatic, HR-positive, HER-negative breast cancer. They also suggest that

testing combinations of ribociclib with other inhibitors of various signalling pathways might lead to additional progress in the management of several subtypes of breast cancer.

Biomarker analyses from the PALOMA-2 trial of palbociclib plus letrozole in postmenopausal women with ER-positive/HER2–negative advanced breast cancer

Lead investigator Richard Finn, MD, from the Jonsson Comprehensive Cancer Center at UCLA, presented results of a biomarker analysis conducted on samples from 568 (85%) patients participating in the phase II PALOMA-2 trial. Of these, 566 samples were evaluable. PALOMA-2 compared the combination of palbociclib and letrozole to letrozole alone as a frontline treatment for postmenopausal women with ER-positive, HER2-negative advanced breast cancer. The combination nearly doubled the median progression-free survival (PFS) over letrozole; median PFS was 24.8 versus 14.5 months, hazard ratio [HR], 0.58 ($p < 0.001$) with combination versus monotherapy, respectively.

The biomarker analyses reported at ESMO 2016 was done to identify potential markers of clinical response and used tumour tissues from either the original diagnostic or the metastatic specimen, which were required from all patients. The investigators performed a central blinded analysis using immunohistochemistry (H-score ≥1 defined positivity) for determination of oestrogen receptor expression (ER-positive), retinoblastoma (Rb), p16, cyclin D1, and Ki-67 (proliferative indices based on 15%, 20%, and 40% cutpoints). Central review confirmed that 89% of samples were ER-positive. In the palbociclib plus letrozole cohort, the ER median (interquartile range) H-score was 120 (range: 45 to 170) versus 110 (range: 38 to 158) with placebo plus letrozole. By H-scores, PFS improvement with palbociclib/letrozole was observed across all ER quartiles. In Rb positive patients, which represented more than 90% of the intent-to-treat (ITT) population, median PFS was 24.2 versus 13.7 months, HR 0.53 ($p < 0.0001$). Patients that were p16-positive represented 85% of the ITT population and showed median PFS of 24.8 versus 13.8 months, HR 0.52 ($p < 0.0001$).

A trend was noted in the 56 patients that were p16 negative towards a benefit with palbociclib plus letrozole but no conclusion could be drawn for 29 Rb negative patients. Cyclin D1 was expressed in 97% of tumour samples but the benefit did not vary with H-score and Ki-67 index values did not identify a cohort that had better or worse PFS with combination treatment over letrozole alone. NCT01740427. Finn *et al.* Abstract LBA15

Practice point and future research opportunities

Palbociclib inhibits CDK4/6 thereby preventing DNA replication by blocking progression from G1 to S phase during cell division and tumour cell proliferation through control of the cell cycle. The rationale for the combination of an aromatase inhibitor with palbociclib stemmed from early preclinical evidence suggesting that CDK4/6 is more active in patients with ER-positive breast cancer, as a result of an intact Rb-pathway. This is consistent with results from this biomarker analysis showing a benefit from adding a CDK4/6 inhibitor in ER-positive patients. However, no additional markers for benefit from palbociclib/letrozole emerged from this analysis.

Improved PFS with fulvestrant over anastrozole in HR-positive advanced breast cancer

Matthew Ellis, Lester and Sue Smith Breast Center, Baylor College of Medicine in Houston, Texas, USA presented findings that showed progression-free survival (PFS) was significantly increased with fulvestrant in women with hormone receptor (HR)-positive advanced breast cancer. Fulvestrant is a selective oestrogen receptor (ER) degrader that targets the HR without affecting oestrogen levels. Dr. Ellis and colleagues conducted a double-blind, multi-centre phase III trial that enrolled 462 women with inoperable locally-advanced or metastatic ER-positive, HER2-negative breast cancer. The women, who had not received prior hormone therapy, were randomised to 500 mg intramuscular injections of fulvestrant on days 0, 14, 28, and then every 28 days (n=230), or to 1 mg of anastrozole daily (n=232). All patients were also allowed one line of chemotherapy.

Median PFS by RESIST 1.1 (primary endpoint) after a median follow-up of 25 months was 16.6 months in patients receiving fulvestrant compared with 13.8 months in patients receiving anastrozole; patients in the fulvestrant arm had a statistically significant 21% improvement in PFS (p = 0.048). The results with fulvestrant were particularly impressive in patients with less aggressive lower-volume disease where PFS was 22.3 versus 13.8 months in patients receiving fulvestrant over those on anastrozole in patients with non-visceral disease who did not show liver or lung involvement at baseline. The objective response rate was 46.1 with fulvestrant and 44.9% with anastrozole, odds ratio 1.07; 95 % confidence interval [CI] 0.72, 2.61 (p = 0.729), and the median duration of response was 20 versus 13.2 months in the respective groups. Death occurred in 29.1% of fulvestrant versus 32.3% of anastrozole patients, hazard ratio 0.88; 95% CI 0.63, 1.22 (p = 0.428)

Both treatment arms showed a similar health-related quality of life. The most commonly reported adverse events (AEs) were arthralgia, which occurred in 16.7% versus 10.3%, and hot flushes in 11.4% versus 10.3% of patients receiving fulvestrant and anastrozole, respectively. NCT01602380. Ellis *et al.* Abstract LBA14_PR

Practice point and future research opportunities

These phase III trial results represent an important advance in the treatment of the most common form of breast cancer, and suggest a potential benefit for using fulvestrant earlier in a patient's treatment. These results confirm the superior efficacy of fulvestrant over anastrozole in postmenopausal women with hormone receptor (HR)-positive locally advanced or metastatic breast cancer who have not received prior hormonal therapy. Physicians would typically choose endocrine therapy as a first approach in patients with non-visceral disease; these findings suggest that fulvestrant could be a new standard of care compared to anastrozole, since the two treatments are tolerated similarly well.

However, since the design of the study, the standard of care for women with this type of disease has moved on to the CDK4/6 inhibitor, palbociclib, in combination with an aromatase inhibitor, for this group of patients. Fulvestrant may be a preferred option for women with non-visceral breast cancer, where particularly strong results were seen with fulvestrant, or for older patients who require a treatment with low toxicity.

Safety and efficacy findings from the Heritage phase III trial of the proposed trastuzumab biosimilar Myl-1401O

Trastuzumab markedly improves survival in women with HER2-positive breast cancer, but the high cost makes it unavailable to many women. Hope S. Rugo, University of California San Francisco Comprehensive Cancer Center and colleagues evaluated the biosimilar, MYL-1401O, for equivalence to the reference drug, trastuzumab, with the goal that introduction of a biosimilar will expand patient access to this effective drug. The investigators conducted the Heritage randomised, double-blind, phase III trial in 500 treatment-naive women with metastatic, HER2-positive breast cancer at 95 sites across Asia, Latin America, and Europe. The women were randomised to first-line treatment with a taxane (docetaxel or paclitaxel, per investigator's choice) plus MYL-1401O or to a taxane plus trastuzumab for at least eight cycles. Patients with stable disease after 8 cycles continued their assigned treatment.

The regulatory requirements for a biosimilar include demonstration of structural and functional similarity to the reference product, similar pharmacokinetics and pharmacodynamics, and confirmed similar safety, efficacy, and immunogenicity. After 24 weeks of treatment, data from 458 women were evaluable which revealed that the biosimilar demonstrated comparable efficacy, safety, and immunogenicity to the reference product, meeting the primary endpoint. The primary endpoint, objective response rate (ORR) by RESIST1.1 was met; ORR was 69.6% for MYL-1401O compared to 64% for branded trastuzumab. The difference in ORR was 5.5%, which fell within the equivalency range. The ratio of ORR was 1.09; confidence intervals [CI] at 2 limits were both within the pre-defined equivalence margin (90% CI 0.974, 1.211) and (95% CI 0.954, 1.237). Median progression-free survival was assessed with a minimum follow up of 48 weeks and was not statistically different at 11.1 months in both arms, hazard ratio [HR] 0.96 (95% CI 0.730, 1.261; log rank p = 0.764). Median overall survival (OS) had not been reached in either arm; however, 48 week-OS rates were 89.1% and 85.1% for MYL-1401O and trastuzumab, respectively.

Immunogenicity and safety were comparable between treatment arms. The rate of serious adverse events was 39.3% in the biosimilar arm versus 37.0% in the trastuzumab arm. Neutropenia was the most common serious adverse event in both arms. Six and 4 fatal events occurred in the MYL-1401O and trastuzumab arms, respectively. EudraCT No: 2011-001965-42. Rugo *et al.* Abstract LBA16

Practice point and future research opportunities

For regulatory approval, the FDA requires the primary endpoint to be ORR ratio, whereas the European Medicines Agency (EMA) requires it to be the difference in ORR. The trastuzumab

biosimilar is not yet FDA-approved, but it appears that 24-week results met FDA requirements of ORR ratio and Myl-1401O appears to be equivalent to trastuzumab when given in combination with a taxane as first line therapy for metastatic breast cancer. Safety, immunogenicity and pharmacokinetic data were also comparable between the biosimilar and reference product.

Just one oncology biosimilar has been FDA-approved thus far, filgrastim-sndz which is marketed for about 15% less than the reference product in the United States. The EMA approved pegfilgrastim biosimilar costs about 25% less than the reference product.

These results of this study show potential ists to broaden access to a lifesaving agent.

Phase I trial results show trastuzumab biosimilar candidate BCD-022 is equivalent to trastuzumab in patients with HER2+ metastatic breast cancer

Maria Shustova, Medical Department, JSC "BIOCAD", St. Petersburg, Russian Federation, and colleagues conducted a trial of BCD-022, a trastuzumab biosimilar, which has already demonstrated equivalence to trastuzumab in a comprehensive comparability physicochemical, non-clinical pharmacokinetic (PK) and pharmacodynamic studies. Dr. Shustova presented findings from an international multicentre randomised double blind PK clinical study that was carried out in patients with HER2-positive metastatic breast cancer. The phase I study randomised 126 patients in a 1:1 ratio to receive either BCD-022 or trastuzumab at a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg in combination with paclitaxel at 175 mg/m^2 every 3 weeks for up to 6 cycles of therapy or until progression or unbearable toxicity.

The objective response rate (ORR), the trial's primary endpoint, was similar in the treatment arms; ORR was 53.57% (95% confidence interval [CI] 40.70%, 65.98%) in the BCD-022 group compared to 53.70% (95% CI 40.60%, 66.31%) with trastuzumab. On the lower end of the spectrum, BCD-022 statistically showed that it was not inferior to trastuzumab since the lower limit of the 95% CI for the difference in ORR between the groups (-19.83%) did not exceed the non-inferiority margin.

No differences between the groups were observed for all other efficacy parameters. Complete response was achieved by 5.36 versus 3.70%, partial response by 48.21% versus 50.00%, and stable disease was reported for SD 25.00% versus 25.93% of patients in the BCD.022 versus trastuzumab arms, respectively. In all, 21.43% of patients receiving BCD-022 compared to 20.37% of trastuzumab patients experienced disease progression.

The adverse event (AE) profiles of BCD-022 and trastuzumab were equivalent; no statistically significant difference was observed between the treatment arms in the rate of all observed AEs, including severe AEs. The investigators determined that the majority of AEs were chemotherapy-associated; the most commonly reported AEs that occurred in 40% or more in either group included neutropenia (73.02% versus 73.77%), anaemia (82.54% versus 77.05%), leukopenia (73.02% versus 68.85%), lymphopenia (69.84% versus 65.57%), hyperglycaemia (57.14%

versus 70.49%), ALP increase (38.68% versus 42.62%), AST increase (42.86% versus 42.62%), and increased ALT (33.33% versus 40.98%), Trastuzumab-specific cardiovascular events included tachycardia (34.92% versus 19.67%), and arterial hypertension (20.63% versus 18.03%), which occurred in BCD-022 versus trastuzumab, respectively. Other trastuzumab-specific cardiovascular events that occurred only in the trastuzumab arm were atrial fibrillation at 3.28%, and extrasystoles at 1.64%) whereas CAD grade 1 occurred at 1.59%, and aggravated myocardiodystrophy occurred at 1.59% only with BCD-022. Binding antibodies with neutralizing activity were detected in just one patient in each group, indicating the low immunogenic potential of both drugs. Shustova *et al.* Abstract 224PD

Practice point and future research opportunities

Trastuzumab is an important drug for treating HER2-positive metastatic breast cancer and biosimilars could cost less and make treatment available to far more women. In this phase I study, BCD-022 showed non-inferiority to trastuzumab in ORR rate and other efficacy parameters also were equivalent between the agents. Both medications demonstrated comparable safety and immunogenicity findings. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have guidelines for obtaining marketing authorisation of biosimilars. An agent is considered a biosimilar if it is proven to be highly similar to an already approved biologic therapy, based upon analytical, animal, and clinical studies assessing immunogenicity, pharmacokinetics or pharmacodynamics. Thus biosimilars could be considered interchangeable if they demonstrate similar clinical outcomes compared with the reference product in a larger clinical trial, such as a phase III study. Results from the next step in testing BCD-022 are anticipated.

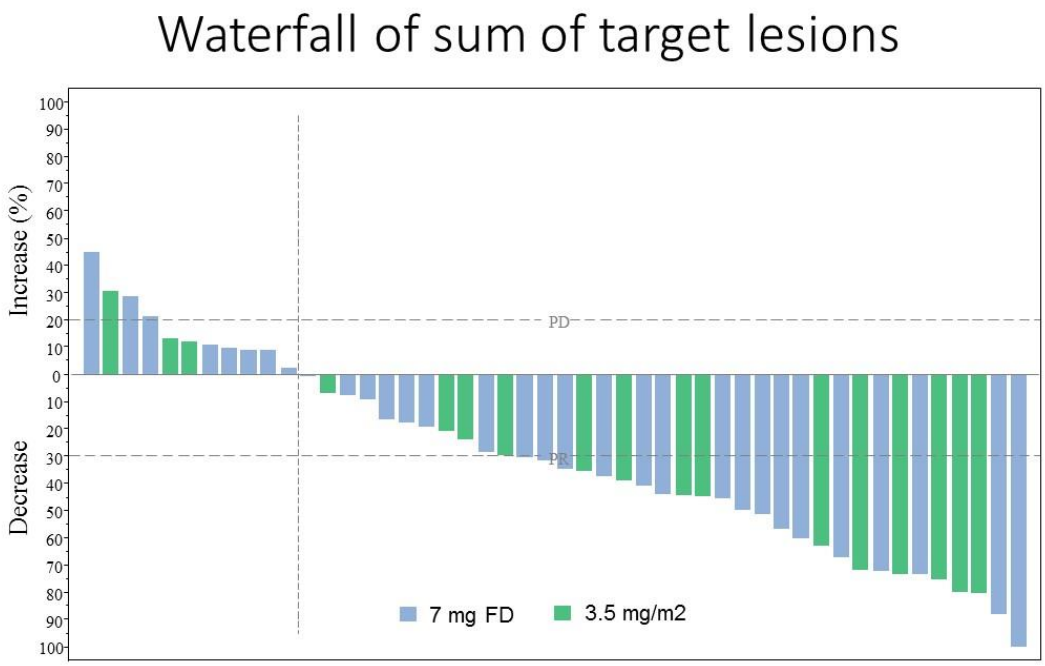
Lurbinectedin demonstrates clinical benefit in patients with BRCA mutation positive metastatic breast cancer and proceeds to phase III trial evaluation

Lead investigator Judith Balmaña, Department of Medical Oncology, Hospital Vall d'Hebron and Vall d'Hebron Institute of Oncology in Barcelona, Spain, presented findings from a phase II trial of lurbinectedin in 54 patients with BRCA mutation positive measurable metastatic breast cancer per RECIST v1.1. BRCA1 mutations were documented in 30 patients and 31 patients had triple negative breast cancer. The patients' median age was 43 years. The patients had performance status ≤ 1, and 30 patients were performance status 0. More than 2 metastatic sites were identified in 33 patients. The patients had a median of one prior chemotherapy treatment for advanced disease; additionally, 45 patients had received prior anthracyclines, 47 received taxanes, 27 received platinum, and 9 had been treated with PARP inhibitors. Lurbinectedin was initially to be administered to all patients at 7 mg fixed dose by i.v. every 3 weeks but the dose was changed by protocol amendment to 3.5 mg/m^2 for improved safety. In all, 35 patients received 7 mg of lurbinectedin and 19 patients were treated with 3.5 mg/m^2.

Lurbinectedin (PM01183) blocks trans-activated transcription by binding to the minor groove of DNA. Activity has been demonstrated in patients with diverse tumour types, and in those that are resistant to platinum-based chemotherapy. Observations that lurbinectedin was active against homologous-recombination-deficient cell lines led investigators to test it in patients with

metastatic breast cancer having deleterious germline BRCA mutations.

Lurbinectedin had been administered to 54 patients as of May 2016, with patients receiving a median of 6 (range: 1 to 24) treatment cycles. The trial met the primary endpoint of confirmed overall response rate (ORR) by RECIST v1.1 Of 54 patients with evaluable data, the ORR was 39% (95% CI 26, 54) in patients receiving the fixed dose, and 44% in patients dosed at 3.5 mg/m^2, with an overall response rate of 40.7% (95% CI 27, 55). The best overall response with lurbinectedin included complete response in one (2%) patient, partial response in 21 (39%) patients, and stable disease in 23 (43%) patients. Just 9 (17%) patients with advanced metastatic breast cancer experienced progressive disease. The median duration of response was 6.7 months (95% CI 3.0, 11.3) and progression-free survival was 4.1+ months (95% CI 2.8, 5.9). Platinum pre-treated patients demonstrated an ORR of 26% (95% CI 11, 26).



Waterfall of sum of target lesions.

© Judith Balmaña.

The most commonly reported grades 3/4 adverse events (AEs) in the subgroup receiving lurbinectedin at the 7 mg fixed dose included neutropenia in 71% of patients and grade 4 neutropenia, which was seen in 51%. Febrile neutropenia occurred in 29%, thrombocytopenia, and transaminase increase were each seen in 26% of patients. Grade 4 thrombocytopenia, and transaminase increase occurred in 20%, and 3% of patients respectively. Grade 3 fatigue and nausea occurred in 17% and 9% of patients, respectively. At the reduced dose, AEs included neutropenia in 50% of patients, febrile neutropenia and thrombocytopenia in 6% each, transaminase increase occurred in 11%, and grade 3 fatigue and nausea occurred in 17% and 6%, respectively. Grade 4 neutropenia was seen in 5% of patients but no other grade 4 AEs occurred in this cohort. Based on these results, a phase III trial of lurbinectedin is planned. Balmaña *et al.* Abstract 223O

Practice point and future research opportunities

Findings from this phase II trial demonstrate that lurbinectedin (PM01183) has activity in BRCA mutation positive metastatic breast cancer regardless of prior platinum treatment. Lurbinectedin blocks trans-activated transcription and activity has been also demonstrated in patients with diverse tumour types, and in those showing resistance to platinum-based chemotherapy.

Tolerance to lurbinectedin improved at the lower 3.5 mg/m^2 dose without compromising efficacy; indeed, the primary endpoint of ORR was met at both dose levels and was highest in the cohort receiving the reduced dose. Based on these results and on predefined criteria of 17 or more confirmed responses in the cohort of evaluable patients, further development of lurbinectedin in patients with BRCA mutation and metastatic breast cancer is warranted and lurbinectedin is being taken forward to a phase III trial in this indication.

Evaluation of the CTC count as a basis for clinical choice of first-line hormone therapy or chemotherapy for HR-positive, HER2-negative metastatic breast cancer

Francois-Clement Bidard, Medical Oncology, Institut Curie, Paris, France, explored the clinical applications of the circulating tumour cell (CTC) count in patients with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer and its utility in clinical decisions. Prognostic factors are generally used in choosing between front-line hormone therapy, the preferred option, or chemotherapy; however, recent reports indicate that the CTC count better informs this decision. Professor Biddard and colleagues compared these strategies in the STIC CTC trial, a large multicentre phase III randomised trial. The investigators evaluated whether the front-line treatment type was best chosen according to clinician decision or by CTC levels.

This analysis was performed on 530 patients whose clinical and pathological characteristics were registered at the time of study inclusion, together with the *a priori* treatment of hormone therapy or chemotherapy that was preferred by clinicians in each patient according to these demographics. CTC count was done using CellSearch® and patients were randomised to receive *a priori* treatment or CTC-driven treatment comprised of hormone therapy when CTC levels were <5 CTC/7.5ml or chemotherapy if CTC counts were higher. In addition to standard statistical tests, multiple correspondence analysis (MCA) was also used to detect and represent

underlying structures in the dataset. Many patients had adverse prognostic factors; 7% of patients had performance status 2 or 3, 34% had 3 or more metastatic sites, 39% had lymphocytopenia, and metastasis to the liver or pleuropulmonary region were identified in 20% and 37% of patients, respectively. Hormone therapy was the *a priori* treatment for 371 (70%) and chemotherapy was decided for 159 (30%) patients.

Patient characteristics that independently associated with the *a priori* choice included age ($p = 0.01$), treatment centre ($p < 0.001$), prior (neo)adjuvant chemotherapy (hazard ratio [HR] 0.47 favouring chemotherapy; $p = 0.02$), elevated SGOT (HR 0.41; $p < 0.001$), liver metastasis (HR 0.45; $p = 0.005$) and bone-only metastasis (HR 3.16 favouring hormone therapy; $p < 0.001$), and a disease-free interval more than 10 years (HR 3.45; $p = 0.003$).

In MCA, the first 2 axes were CTC count and the receipt of prior chemotherapy for early breast cancer, and the other clinical and pathological factors were distributed accordingly. Elevated CTC counts (≥5 CTC/7.5ml) were detected in 205 (39%) patients. Among the 263 patients randomised to the CTC-driven decision arm, *a priori* hormone therapy was decided for 186 (71%) patients that was confirmed in 122 (68%) patients and later switched to chemotherapy in 58 (32%) patients. The decision for *a priori* chemotherapy was made for 77 (29%) that was confirmed in 35 (49%) patients and then switched to hormone therapy in 37 (51%) patients. Bidard *et al.* Abstract 226PD

Practice point and future research opportunities

In the absence of any predictive factor, treatment decision is influenced by numerous prognostic factors and CTC can provide different and complementary data. Patient follow-up is ongoing to compare the outcome of patients with HR-positive, HER2-negative metastatic breast cancer whose treatment was CTC-driven compared to treatment based on the *a priori* clinical decision.

BRAF genomic alterations in metastatic breast cancer

Joan Albanell, Cancer Research Program, Institut Hospital del Mar d'Investigacions Mèdiques in Barcelona, Spain, investigated whether defining BRAF genomic alterations in metastatic breast cancer could identify druggable targets. The genomic alterations included base substitutions, indels, copy number alterations (CNA) and fusions/rearrangements. Dr. Albanell and colleagues extracted DNA from 40 microns of FFPE sections obtained from 7850 tumours to perform comprehensive genomic profiling (CGP) on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 579X for up to 315 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. The investigators identified 83 (1.1%) patients with BRAF-altered breast cancer, with a mean age of 57 years (range: 32 to 84 years). There were 39 ductal, one inflammatory, 3 metaplastic, 2 lobular, and 38 NOS tumours. The primary tumour could be used for CGP in 29 (34.9%) cases and tumours from metastatic sites including lymph nodes, liver, bone, lung, brain adrenal, and soft tissue was used in 54 (65.1%) cases.

CGP revealed BRAF genomic alterations that could possibly lead to aberrant MAPK signalling; 51.8% of cases contained BRAF amplifications, 15.7% had base substitutions in V600E, 3.6% had K601E base substitutions, 21.6% of cases had other missense base substitutions, and 6.0% of cases harboured fusions (6.0%). Three (3.6%) additional mutations were identified that are uncharacterised for their effect on BRAF signalling activity. Of the fusions identified, 2 were KIAA1549-BRAF, one each of AGK-BRAF, FCHSD2-BRAF, and KLHDC10-BRAF was found. Tumours harbouring a BRAF amplification or base substitution genomic alteration also showed a statistically significant reduction in ERBB2 mutations.

Targetable genes that were more commonly amplified in tumours with BRAF genomic alteration compared to BRAF wild-type breast cancer, include CDK6 ($p = 0.001$), HGF ($p < 0.001$), and MET ($p < 0.001$). Although BRAF genomic alterations are uncommon in breast cancer and have been identified in 1.1% of cases, targetable base substitutions and rare fusions were identified. BRAF genomic alterations in metastatic breast cancer more commonly occur in HER2-negative and triple negative breast cancer. Alban ell, *et al.* Abstract 228PD

Practice point and future research opportunities

This study found that BRAF genomic alterations were rarely present in metastatic breast cancer but did identify alterations that were potentially targetable with currently available drugs, particularly in triple negative breast cancer. Continued study of BRAF alterations in breast cancer is warranted.

Comprehensive genomic profiling reveals therapeutically targetable molecular subtypes of breast carcinomas

Lead Jeffrey S. Ross, Pathology, Albany Medical Center in Albany, USA, and colleague evaluated whether comprehensive genomic profiling (CGP) could be used to reveal targetable genomic alterations, and also redefine breast carcinoma classification into therapeutically relevant subtypes as an alternative to the hormone receptor (HR) expression-based classifications of basal, luminal A, luminal B, and HER2 overexpressed. Clinically relevant genomic alterations (CRGA) are those linked to drugs on the market or under evaluation in clinical trials. DNA was extracted from 40 µm of FFPE sections obtained from 8654 consecutive breast cancer patients. CGP was performed on hybridization-captured, adaptor ligation-based libraries (mean coverage >500X) for up to 315 cancer-related genes. Total mutational burden (TMB) was determined on 1.2 Mbp of sequenced DNA.

CGP revealed 6959 (80.4%) tumours harboured a genomic alteration in at least one pathway, and 2697 (31.2%) breast cancer tumours harboured alterations in just one pathway. The investigators found that several distinct pathways are altered in breast cancer, making them potentially targetable with therapies that are already FDA approved for oncology indications. The ERBB pathway was altered in 1294 cases, suggesting that trastuzumab, pertuzumab, afatinib, lapatinib, and neratinib could have activity against tumours with these alterations. Alterations in the PI3K/AKT/mTOR pathway occurred in 4375 cases, making them potentially targetable with everolimus and temsirolimus, whereas palbociclib could be active against alteration in the CDK

pathway that were detected in 2685 cases. A total of 2650 case showed alterations in the FGFR pathway, making these tumours potentially susceptible to pazopanib or ponatinib. Mutations in other targetable kinases such as RET, ROS1, and RAF were found in 424 cases, meaning they could be sensitive to sorafenib, regorafenib, dabrafenib, vemurafenib, crizotinib, cabozantinib, or sunitinib. Fulvestrant and tamoxifen may be putative agents targeting the 792 cases harbouring ESR1 mutations, which confer hormone therapy resistance in breast cancer. Olaparib could have activity in the1266 cases that were identified as homologous recombination deficient. Immunotherapy sensitivity, defined as TMB >20 mut/Mbp or mutation of specific DNA repair pathways was identified in 419 cases that could make these tumours druggable with pembrolizumab, nivolumab, atezolizumab, or ipilimumab. In addition, homologous recombination deficiency, defined as mutation of the BRCA genes, other genes in the FANC complex, or DNA repair genes, have all been shown to confer sensitivity to PARP inhibitors.

To underscore the utility of CGP, the investigators pointed out that only 9.8% of breast cancer tumours would be HER2-positive by immunohistochemistry. Ross *et al.* Abstract 229PD

Practice point and future research opportunities

Comprehensive genomic profiling was successfully used to identify clinically relevant genomic alterations allowing for stratification of tumours according to predicted sensitivity to a variety of therapies. The majority (80%) of breast cancer tumours harbour targetable genomic alterations, many of which would not be identified by immunohistochemistry or hotspot testing, but are detectable by next-generation sequencing. Comprehensive genomic profiling is a powerful tool to guide treatment across therapeutically distinct, but targetable, pathways. More trials wherein patients with breast cancer are stratified and treated according to comprehensive genomic profiling results are anticipated.

CENTRAL NERVOUS SYSTEM MALIGNANCIES

Molecular characterisation of risk factors in low-grade gliomas

Enrico Franceschi, Medical Oncology, Bellaria - Maggiore Hospitals, Azienda USL - IRCCS Institute of Neurological Sciences in Bologna, Italy, presented findings on behalf of the Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO) from a molecular characterisation of IDH1/2, 1p/19q codeletion, and MGMT methylation status in low grade gliomas (LGG). Data from all adult LGG patients in the database of the institution who received surgery and had sufficient tissue for biomarker characterisation were evaluated for outcome. IDH1/2 assessment was performed on FFPE samples by PCR, MGMT was assessed by methylation specific PCR, and 1p/19 codeletion by FISH.

The study comprised 198 consecutive patients with LGG, with a median age of 38 (range: 18 to 72) years. The majority, 109 (55.1%) patients were younger than 40 years of age. Biopsy was done in 26 (13.1%) patients, 119 (60.1%) patients underwent partial resection, and 53 (26.8%) patients had complete resection. Twenty-eight patients (14.1%) were considered low risk (<40 years with complete resection). IDH1/2 mutation was found in 79.8% of patients, 1p/19q codeletion was found in 41.4% of patients, and MGMT methylation was seen in 57.1% of patients. A subgroup of 28 patients was considered to be at low risk of recurrence that were aged < than 40 years and had undergone complete resection.

At a median follow-up of 74.0 months, an evaluation of patient outcome revealed that median survival in low risk patients was 211.0 months (95% confidence interval [CI] 190.4, 231.6) compared to 145.3 months (95%CI 108.5,182.2) in high-risk patients (p = 0.006). Median survival for patients with IDH1/2 mutation was 159 months (95%CI 103.3, 214.7) versus 87.9 months in patients with IDH1/2 wild type (95%CI 61.1, 114.6; p < 0.001). On multivariate analysis clinical risk (p = 0.006), IDH1/2 mutation (p < 0.001), and 1p/19q codeletion (p = 0.03) emerged as biomarkers that significantly correlated with overall survival; however, MGMT methylation was not statistically significant. Franceschi *et al.* Abstract 323O

Practice point and future research opportunities

This study demonstrated that molecular characterisation of low-grade glioma can be used to identify prognostic markers that define the outcome of this disease; clinical risk, IDH1/2 mutation, and 1p/19q codeletion significantly associated with survival. Moreover, clinical risk assessment continues to play an important role.

ANG1005, a novel peptide-paclitaxel conjugate that crosses the BBB demonstrates clinical benefit in patients with recurrent CNS metastasis from breast cancer

Lead author Shou-Ching Tang, Georgia Regents University Cancer Center, Augusta University, Augusta, USA, presented findings from an open label phase II clinical study testing the activity

of ANG1005, a novel taxane derivative comprised of 3 paclitaxel molecules covalently linked to Angiopep-2, a peptide designed to cross the blood-brain and blood cerebrospinal fluid barriers via the LRP-1 transport system. ANG1005 was designed to penetrate malignant cells in the central nervous system (CNS) and was evaluated in 72 patients with metastatic breast cancer and recurrent brain metastasis, including patients with blood/cerebrospinal fluid metastasis (BCBM) and newly diagnosed leptomeningeal carcinomatosis (LC). ANG1005 was administered i.v. at 600 mg/m^2 every 3 weeks and HER2-positive patients were allowed to continue trastuzumab with/without pertuzumab. Intracranial response was assessed by Gd-MRI using CNS RECIST 1.1, and extracranial response was evaluated per RECIST 1.1. The patients' median age was 47.5 (range: 26 to 76) years. A median of 6 (range: 1 to 29) prior therapies for breast cancer had been received by the patients, with 84% of patients receiving prior taxane treatment. Prior therapy for brain metastasis included cranial surgery and/or radiation for 87% of patients, and 19% patients received systemic therapies.

The analysis was done on 72 patients in the safety population and 58 patients with evaluable data in the efficacy population. The best intracranial response following ANG1005 treatment in the efficacy population included 8 (14%) patients with partial response (PR), 3 (5%) of which were confirmed. Stable disease was reported in 33 (57%) patients. Extracranial tumour responses included one (3%) complete response (CR), 2 (7%) PRs, and 24 (80%) patients achieved SD among the 30 evaluable patients, which included the 93% of patients that had received prior taxane therapy. The 6-month overall survival (OS) rate was 63.6 % (95% confidence interval [CI] 42.9, 78.5) for patients with LC. In contrast, the Kaplan-Meier estimated median OS was 34.6 weeks (95% CI 24.1, 40.9) from first ANG1005 treatment for LC patients. Following ANG1005 treatment, improved CNS clinical symptoms were reported, including in LC patients. Safety was similar to that of paclitaxel, with myelosuppression as the predominant toxicity. NCT02048059. Tang *et al.* Abstract 324O

Practice point and future research opportunities

Novel ANG1005, a taxane derivative plus paclitaxel that was designed to cross the blood brain and blood cerebrospinal fluid barriers demonstrated activity in previously treated breast cancer metastasis located both within and outside of the central nervous system. Patients with leptomeningeal carcinomatosis experienced clinical benefit of an estimated median OS of approximately 8 months, which doubled the historical median of about 4 months following therapy. The results from the planned randomised study are awaited.

Routine molecular subgrouping of medulloblastoma for clinical applications using low-cost, mass spectrometry-based DNA methylomics

Ed Schwalbe, Paediatric Neuro-Oncology, Northern Institute for Cancer Research University of Newcastle, Newcastle Upon Tyne, UK, and colleagues evaluated an array-independent, robust subgrouping assay suitable for routine quality-controlled subclassification, including scant, poor-quality, aged samples that they developed, with the intent of making subclassification of

medulloblastoma by DNA methylation patterns cost effective and feasible in the clinic to inform treatment decisions. DNA methylation patterns allow the categorisation of medulloblastoma into 4 molecular subgroups; in this study, the investigators tested the utility of the microarray on data from the PNET4 trial. Using a cross-validated classification model, a minimal, multiply-redundant, 17-locus signature was derived to assign subgroup from 220 MBs profiled using Illumina 450k DNA-methylation arrays. The investigators then adapted the MALDI-TOF Mass Spectrometry (MassARRAY, Agena Bioscience) iPLEX assay to interrogate DNA methylation following bisulfite treatment. After in vitro validation, the assay was applied to 101 DNA extracts from FFPE and nuclear (<30,000 nuclei) tumour material. Subgroup assignments from an optimised classifier were compared against gold-standard 450k calls. Following validation, subgrouping was attempted for standard-risk PNET4 samples where possible.

A total of 95 of the 101 validation samples had high-confidence assignments which recapitulated 450k subgroup calls. Subsequently, high-confidence calls could be made for 107 of 153 PNET4 samples. Notably, a worse survival was observed for standard-risk PNET4 group 4 patients (80% event free survival rate; p = 0.01). SIOP-PNET4: NCT01351870. Schwalbe *et al.* Abstract 325O

Practice point and future research opportunities

This study used data from the PNET4 trial to demonstrate that routine subtyping of medulloblastoma can be performed using minimal DNA methylation signatures. The assay is suitable for reliable, robust testing of poor-quality, degraded samples using <100ng DNA. The assay's low-cost, rapidity and application to single samples demonstrate its potential for routine use. It can be retrospectively applied to archival cohorts where material is scant to contemporise historical studies. This first demonstration of multiplexed, methylation subtyping holds promise for future molecular subclassification and prognostication across diverse tumour types using methylomics.

Meta-analysis of pooled data reveals improved PFS only with bevacizumab but no OS benefit with antiangiogenic drugs in glioblastoma

Giuseppe Lombardi, and colleagues at the U.O.C. Oncologia Medica 1, Veneto Institute of Oncology- IRCCS in Padua, Italy evaluated the efficacy of antiangiogenic drugs in patients with glioblastoma, which are highly vascularised tumours, in this meta-analysis. MEDLINE, WEB of SCIENCE, ASCO, ESMO and SNO databases were search for relevant published and unpublished randomised controlled trials (RCTs) of antiangiogenic drugs versus chemotherapy in patients with glioblastoma from 2000 to January 2016. The investigators reviewed progression-free survival (PFS) and overall survival (OS) in 4566 patients with glioblastoma receiving antiangiogenic agents as first or second-line therapy and with chemotherapy. In all, 16 RCTs were included, 9 testing bevacizumab, 2 cilengitide, and 1 trial each of enzastaurin, dasatinib, vandetanib, temsirolimus, and cediranib.

Taken together, the analysis of data from all trials revealed no improvement in OS, with a pooled hazard ratio [HR] of 1.02 (95% confidence interval [CI] 0.93, 1.1; p = 0.7). The 7 RCTs wherein

a different antiangiogenic was tested showed no improvement in OS over standard treatment, pooled HR 1.05 (95% CI 0.89,1.23; p = 0.5).

In particular, bevacizumab did not improve OS; in 2752 patients participating in 9 trials the pooled HR for OS was 0.98 (95% CI 0.89, 1.08; p = 0.7). An assessment of OS the 2084 patients receiving bevacizumab as first-line in 6 RCTs demonstrated a pooled HR 1.02 (95% CI 0.88, 1.19; p = 0.8), whereas the pooled HR was 0.95 (95% CI 0.77, 1.17; p = 0.6) for OS in the 3 RCTs of second-line bevacizumab. Similarly, no improvement in OS was demonstrated in 2588 patients receiving bevacizumab associated with chemotherapy, pooled HR 0.99 (95% CI 0.88, 1.11; p = 0.8).

An analysis of PFS in 4349 patients treated in 14 RCTs did demonstrate that PFS was statistically prolonged with antiangiogenic drugs; pooled HR 0.73 (95% CI 0.62, 0.86; p < 0.01). However, bevacizumab emerged as the only antiangiogenic drug that demonstrated improved PFS. Data from 2752 patients treated with bevacizumab showed significantly improved PFS, pooled HR 0.6 (95% CI 0.5, 0.7; p < 0.01). This benefit remained consistent across all treatment regimens reviewed, whether bevacizumab was administered as monotherapy, HR = 0.6; CI 95% 0.44, 0.82; p < 0.01) or combined with chemotherapy, HR 0.6; (95% CI 0.4, 0.7; p < 0.01). PFS was significantly improved with first-line bevacizumab, HR 0.65 (95% CI 0.52, 0.83; p < 0.01) or with second-line bevacizumab in recurrent disease, HR 0.51 (95% CI 0.43, 0.61; p < 0.01). Lombardi *et al.* Abstract 328PD

Practice point and future research opportunities

In an effort to resolve the unclear findings from various trials of antiangiogenic drugs in patients with glioblastoma, the authors conducted this large, pooled data meta-analysis. Although glioblastomas are highly vascularised tumours, treatment with antiangiogenic drugs, including bevacizumab, did not improve OS, when administered either as first or second-line treatment.

The PFS was not improved by antiangiogenic drug treatments, except for bevacizumab, which demonstrated a PFS benefit when administered as a single agent, combined with chemotherapy, and also as first or second-line treatment in patients with glioblastoma.

Synchronous breast cancer and meningioma is an indicator of poorer survival

Aiming to determine the possible prognostic relationship between breast cancer and meningioma Catarina Ribeiro, Department of Oncology, Centro Hospitalar Lisboa Central-CHLC-Hospital São Jose, Lisbon, Portugal, and colleagues evaluated the impact on survival of the tumour exposure sequence in patients registered in a large retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database. Patients were stratified according to whether the tumours were synchronous or metachronous into a variable arm, defined as patients diagnosed with meningioma prior to developing breast cancer, or a synchronous arm wherein patients developed both conditions simultaneously, or into an arm of patients diagnosed with breast cancer before meningioma.

The analysis comprised data from 1715 patients with a median follow-up of 84 months. The poorest prognosis and shortest median survival of 32 months was observed in patients diagnosed with breast cancer and meningioma at the same time, whereas women developing breast cancer prior to the onset of meningioma had the longest median survival of 110 months. The unadjusted analysis showed a statistical association between the simultaneous group and the shortest survival, hazard ratio [HR] 3.13 (95% confidence interval [CI] 1.62, 6.04) that was confirmed in the adjusted analysis, HR 3.11 (95%CI 1.58, 6.19). The adjusted analysis also determined that there was no statistical difference between the metachronous tumours, regardless of the sequence.

Poorer survival was also associated with increasing age, HR 1.13; 95%CI 1.11, 1.15 ($p < 0.005$), and the presence of grade III meningioma, HR 4.51; 95%CI 1.90,10.69 ($p < 0.005$). The authors reported that meningioma treatment did not impact survival or breast cancer ($p > 0.05$), whereas the presence of grade III meningioma and hormone receptor status influenced survival in synchronous tumours ($p > 0.05$) but had no influence on survival in women with metachronous tumours ($p < 0.05$) on stratified analysis. Ribiero *et al.* Abstract 329PD

Practice point and future research opportunities

This large analysis revealed that women having a synchronous development and/or diagnosis of breast cancer and meningioma faced the poorest prognosis of shorter survival than women developing both breast cancer and meningioma in a metachronous manner. The sequence of which cancer developed first had no effect on survival, but increasing age also showed an association with poorer survival.

Single agent ibrutinib demonstrates clinical benefit in recurrent/refractory primary and secondary CNS lymphoma

Christian Grommes, Neurology, Memorial Sloan Kettering Cancer Center, New York, USA underscored the need for new treatment options in primary central nervous system lymphoma (PCNSL). Even fewer treatment options are available for recurrent/refractory disease, which carries a poor prognosis with objective response rates (ORR) ranging between 30 to 60% and median progression-free survival (PFS) of just 2 to 5 months.

Dr. Grommes and colleagues assessed the efficacy of ibrutinib in patients with recurrent/refractory PCNSL and secondary CNSL (SCNSL); ibrutinib is a first-in-class oral once-daily targeted treatment that blocks Bruton's tyrosine kinase, which promotes tumour viability and growth. Ibrutinib is approved by the US Food and Drug Administration for the treatment of patients with chronic lymphocytic leukaemia and mantle cell lymphoma.

The trial enrolled 20 adult patients with ECOG performance status ≤2 PCNSL and SCNSL and normal end-organ function. Patients could have had an unrestricted number of CNS-directed prior therapies, but patients with SCNSL plus systemic disease were ineligible. The median age was 69 (range: 21 to 85) years and 12 patients were female. PCNSL was diagnosed in 65% and 35% of patients had SCNSL; 70% of patients had recurrent disease. Parenchymal disease was

reported in 11 patients, 3 had isolated cerebrospinal fluid (CSF) involvement, and 6 patients had both. The prior CNS directed therapy was methotrexate regimens and the median number received was 2. Ibrutinib was administered daily to 3 patients at 560 mg and 17 patients received 840 mg; the mean ibrutinib concentration in the CSF at days 1 and 29 was 1.75 ng/mL (3.97 nM) and 2.51 ng/mL (5.6 nM), which are both above the IC50 of 1nM required in vitro to reduce growth of lymphoma cells.

After a median follow-up of 147 days, 16 of the 20 patients were evaluated for response. The ORR was 65% and included 4 complete response (CR), including 3 patients with CSF involvement and one parenchymal, and 9 partial response (PR). Progressive disease was reported in 3 patients. Response in 3 patients has not been confirmed in a second assessment. The median PFS to date was 5.5 months and the longest is continuing past 13.2 months. Despite clinical and radiographic response, 2 patients withdrew from the study, and one stopped due to a fungal infection.

The most commonly reported toxicities were hyperglycaemia, anaemia, and thrombocytopenia. Four grade 4 toxicities were observed in 4 patients that consisted of lymphopenia in 2 patients, and one patient each had sepsis and neutropenia. Grade 3 toxicities occurred in 10 patients, including lymphopenia in 3 patients, 2 patients each had thrombocytopenia, hyperglycaemia, or lung infection and one patients each had grade 3 neutropenia, urinary tract infection, colitis, and fungal encephalitis. Molecular testing is in process to associate genomic alterations with patient outcome. NCT02315326. Grommes *et al.* Abstract 331PD

Practice point and future research opportunities

This trial demonstrated clinical benefit with ibrutinib in patients with this aggressive cancer, including prolonged PFS beyond that noted in literature. Patients with primary and secondary recurrent/refractory CNS lymphoma tolerated ibrutinib and showed manageable toxicities. Ibrutinib may be a putative therapeutic alternative in this setting that should be further investigated. The ongoing molecular analysis could aid in patient selection.

DEVELOPMENTAL THERAPEUTICS

89Zr-labeled CEA-targeted IL-2 variant immunocytokine in patients with solid tumours demonstrates dose-dependent CEA-mediated tumour accumulation

Findings from a trial of novel CEA-IL2v (cergutuzumab amunaleukin, RG7813), an engineered IL-2 variant antibody directed against carcinoembryonic antigen (CEA) with abolished IL-2 receptor (IL-2R) α (CD25) binding were reported by Catherina W. Menke-van der Houven van Oordt, Medical Oncology, Vrije University Medical Centre in Amsterdam, Netherlands. She explained that CEA-IL2v was designed to improve the pharmacological and safety profile of IL-2 and direct the local accumulation of IL-2 into CEA-positive tumours. This phase I trial was conducted to demonstrate selective and specific tumour targeting by labelling CEA-IL-2v with ^{89}Zr to allow evaluation of biodistribution and tumour accumulation at varying doses in tumours having different levels of CEA. A sub-study of the trial enrolled 25 patients with advanced and/or metastatic solid tumours; 16 patients had CEA-positive and 9 patients had CEA-negative tumours. CEA-IL2v was administered intravenously every 2 weeks at total doses of 6 mg, 20 mg and 30 mg. All patients underwent up to 3 ^{89}Zr-PET assessments during cycle 1, and patients receiving 20 mg showing initial tumour uptake at cycle 1 underwent additional assessments in cycle 4.

At day 5 post injection, accumulation of ^{89}Zr-CEA-IL-2v was observed that was independent of CEA status in lymphoid tissues, including the spleen (SUV_{mean} 10.0±3.1) and non-pathological lymph nodes (SUV_{mean} 2.0±1.2) at all doses. The investigators considered this to represent IL-2 receptor-mediated uptake. Intratumoural accumulation of ^{89}Zr-CEA-IL-2v in cycle 1 was observed in CEA-positive patients, including one of 4 patients receiving the 6 mg dose (SUV_{peak} 5.4), 6 of 8 patients dosed at 20 mg (SUV_{peak} 5.2±2.7), and all 4 dosed at 30 mg (SUV_{peak} 5.8±4.4). By cycle 4, ^{89}Zr-CEA-IL-2v accumulation in tumour lesions was decreased (SUV_{peak} 4.0±1.1). The authors explained this could be due to anti-drug antibodies or an expansion of IL-2R expressing T-cells. In tumours with high accumulation of ^{89}Zr- CEA-IL-2v at cycle 1, there was a trend towards decreased metabolic activity at early FDG-PET evaluation. NCT02004106 EUDRACT NUMBER: 2013-003041-41. Menke-van der Houven van Oordt *et al.* Abstract 358O

Practice point and future research opportunities

The substudy demonstrated that, at all doses, ^{89}Zr- CEA-IL-2v accumulated in spleen and secondary lymphoid tissues, due to IL-2R mediated uptake, and accumulation was dose-dependent in the tumour. The phase I study investigating CEA-IL2v both as monotherapy and in combination with atezolizumab in patients with solid tumours is ongoing.

Avitinib (AC0010) a third generation irreversible EGFR inhibitor shows promise in patients with EGFR TKI-resistant NSCLC

Li Zhang, State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, China presented first-in-human results from a dose escalation study of

avitinib (AC0010), a third generation irreversible epidermal growth factor receptor (EGFR) inhibitor that has been shown to overcome T790M-induced resistance in preclinical studies. Patients with non-small cell lung cancer (NSCLC) and EGFR positive mutation that developed resistance to the first generation EGFR tyrosine kinase inhibitors (TKIs) were enrolled; both T790M positive and negative patients were eligible. Oral AC0010 capsules were administered in 5 cohorts once daily in 50 mg, 100 mg, 200 mg, 350 mg, and 550 mg tablets, and 3 cohorts received twice daily oral doses of 175 mg, 250 mg, and 300 mg. All patients were required to undergo biopsy for genotyping to confirm T790M status prior to treatment and were assessed for pharmacokinetics (PK), overall response rate (ORR), disease control rate (DCR), and adverse events (AEs).

As of 5 May 2016, the study enrolled 51 patients; 49% were female, the median age was 55 years, and 86% of patients were T790M mutation positive. The maximum tolerated dose had not been reached. PK were dose proportional, and the median plasma half-life was 7.8 (range: 7.6 to 8.0) hours. Twice daily dosing method reduced the fluctuation coefficient of the plasma concentration by 0.40 fold, and improved the area under the curve (AUC) by 1.28 fold, compared to once daily dosing. No food effects were observed.

At data cut-off, 48 patients were evaluated in the once daily cohorts that demonstrated an ORR of 41.7%, and the DCR was 75.0%. All responses were observed at dose levels ≥200mg daily. The ORR increased to 57.6% in 33 patients treated daily with avitinib at ≥350mg and DCR was 87.9% in this cohort. The 33 evaluated patients in the twice daily dosing regimen showed a better ORR of 66.7% and DCR of 94.4%. The longest duration of response was 11 months and was ongoing at data cut-off.

Adverse events (AEs) were mostly grade 1 and transient. The most commonly reported drug related AEs grade 3 and higher were rash, which occurred in 4% of patients. ALT/AST elevation in 4%, and 2% of patients had pneumonia (2%). No hyperglycaemia or grade 3 QTc prolongation were observed. NCT02274337 Zhang *et al.* Abstract 359O

Practice point and future research opportunities

These first-in-human results of avitinib (AC0010I), a third generation, irreversible EGFR inhibitor that seems to overcome T790M-induced resistance demonstrated a dose-dependent response in patients with NSCLC. These findings taken together with good safety profile suggest avitinib may have promising anticancer activity for NSCLC patients with T790M mutation who become resistant to first generation TKIs. The ongoing phase I trial is warranted and the results are anticipated.

Phase I results with novel FGFR inhibitor BAY 1163877 show promise in patients selected by tumour mRNA expression

Markus Joerger, Department of Oncology, Cantonal Hospital, St Gallen, Switzerland reported

results from the first-in-human dose escalation study of the potent small molecule pan-fibroblast growth factor receptor (FGFR) inhibitor, BAY 1163877. The novel compound was tested in patients with treatment-refractory locally advanced or metastatic solid tumours in a multicentre phase I study that was conducted in 6 countries. Dr. Joerger and colleagues reasoned that since FGFR expression is de-regulated by both genetic and epigenetic mechanisms, levels of FGFR messenger RNA (mRNA) could be measured to identify patients likely to benefit from FGFR-targeted approaches. The trial comprised a dose-escalation study in 23 patients plus followed by an expansion stage that enrolled 57 patients with high tumour FGFR mRNA levels into 3 expansion cohorts that included patients with bladder cancer, head and neck squamous cell carcinoma (HNSCC), squamous non-small cell lung cancer (sqNSCLC), and all comers.

The dose escalation study tested 5 doses ranging from 50 to 800 mg administered twice daily. BAY 1163877 has a half-life of about 12 hours and revealed less than dose-proportional increase in exposure at doses above 200 mg. A maximum tolerated dose was not defined because there were no dose-limiting toxicities. However, on preclinical results, the effect on serum phosphate levels, and clinical analyses, a twice daily dose of 800 mg was taken forward to the expansion phase.

Clinical benefit in 44 evaluable patients was demonstrated with BAY 1163877 in the expansion cohort that included 6 partial responses (PR) in one patient each with HNSCC, sqNSCLC, adenoid cystic carcinoma of the tongue, and 3 patients with bladder cancer. Stable disease (SD) was achieved by 18 patients lasting more than 12 weeks, with 8 showing SD lasting more than 24 weeks. Most patients, including 4 achieving PR, did not have FGFR genetic alterations.

BAY 1163877 was well-tolerated at doses up to 800 mg twice daily, although most patients developed low-grade hyperphosphatemia, which is seen with all FGFR inhibitors. These patients received treatment with a phosphate binder and/or dose reduction of BAY 1163877.

The authors commented that the innovative biomarker approach effectively identified patients with a good chance to benefit from BAY 1163877 and recommended further studies should be conducted, particularly in bladder cancer where approximately 35% of patients are FGFR mRNA positive. Joerger *et al.* Abstract 360O

Practice point and future research opportunities

Most studies of FGFR inhibitors have looked at FGFR abnormalities in tumours with limited success This study successfully used measurements of tumour FGFR mRNA expression to select patients for the expansion cohort. FGFR inhibitors may provide a therapeutic opportunity to patients with rare tumours. In this patient population, there were some patients with adenoid cystic carcinoma that demonstrated long-term disease control and a high response rate, particularly in bladder cancer. Taken together with the toxicity profile of BAY 1163877, which is better than other FGFR inhibitors under investigation, further study in larger cohorts and confirmation of these results are warranted. In the context of molecular screening programmes, patients with FGFR mRNA expression may be offered the opportunity for treatment with FGFR inhibitors.

ENDOCRINE AND NEUROENDOCRINE TUMOURS

Everolimus and pasireotide LAR alone or in combination significantly improved outcome in patients with advanced lung and thymic carcinoids

Piero Ferolla of the Multidisciplinary NET Group and the Department of Medical Oncology, Umbria Regional Cancer Network and University of Perugia in Perugia, Italy and co-investigators conducted LUNA, the first randomised trial specifically designed for patients with progressive lung and thymic carcinoids that assessed the efficacy and safety of pasireotide LAR and everolimus alone and in combination. The LUNA phase II trial randomised 41 patients to pasireotide LAR at 60 mg/month intramuscular, 42 patients to oral everolimus at 10 mg/day orally, and 41 patients to pasireotide LAR plus everolimus at the same single-agent doses. The patients' median age was 64 years; atypical carcinoid was present in 68.5% of patients while 31.5% of the patients had typical carcinoid. The primary tumour site was the lung in 93.5% of patients, and thymus in 6.5%. WHO performance status was 0, 1, or 2 in 64%, 34%, and 2% of patients, respectively. Prior drug treatment had been administered to 44% of patients, radiotherapy to 27%, surgery/locoregional therapy to 97%, and 48% of patients had received prior somatostatin analogues.

The primary endpoint of the trial was the progression-free rate at 9 months (PFR-9), defined as the proportion of patients with documented complete response (CR), partial response (PR), or stable disease (SD) by RECIST v.1.1 criteria at 9 months. Secondary end points included progression-free survival (PFS), disease control rate (DCR), and safety.

Although the greatest response was observed with the combination, all 3 treatment arms of the LUNA study met the primary end-point: PFR-9, was achieved by 39.0% of patients on single agent pasireotide LAR (95% confidence interval [CI] 24.2, 55.5), 33.3% of patients on sole everolimus (95% CI 19.6, 49.5), and by 58.5% of patients on combined everolimus and pasireotide LAR (95% CI 42.1, 73.7). No CR was observed; the best overall response at 9 months was PR, which was achieved by 2% of patients in each treatment arm. The SD was attained by 34% of pasireotide LAR patients, 31% of everolimus patients, and by 49% of patients receiving the combination. Progressive disease (PD) occurred in 17% receiving pasireotide LAR monotherapy versus 2% of patients receiving sole everolimus. PD was not reported with the combined treatment.

No new safety signals were observed. Study treatment was discontinued by 65% of patients during the 12-month core phase. Discontinuation due to PD or adverse events (AEs) was each reported in 27% of patients. AEs were mostly grades 1/2 across treatment groups. The most common AEs (any grade) with combined pasireotide LAR and everolimus were hyperglycaemia, which was reported in 88% of patients, diarrhoea in 78%, weight decrease in 56%, asthenia in 37%, and stomatitis was reported in 34% of patients. EUDRACT number: 2011-002872-17. Ferula *et al.* Abstract 416O

Practice point and future research opportunities

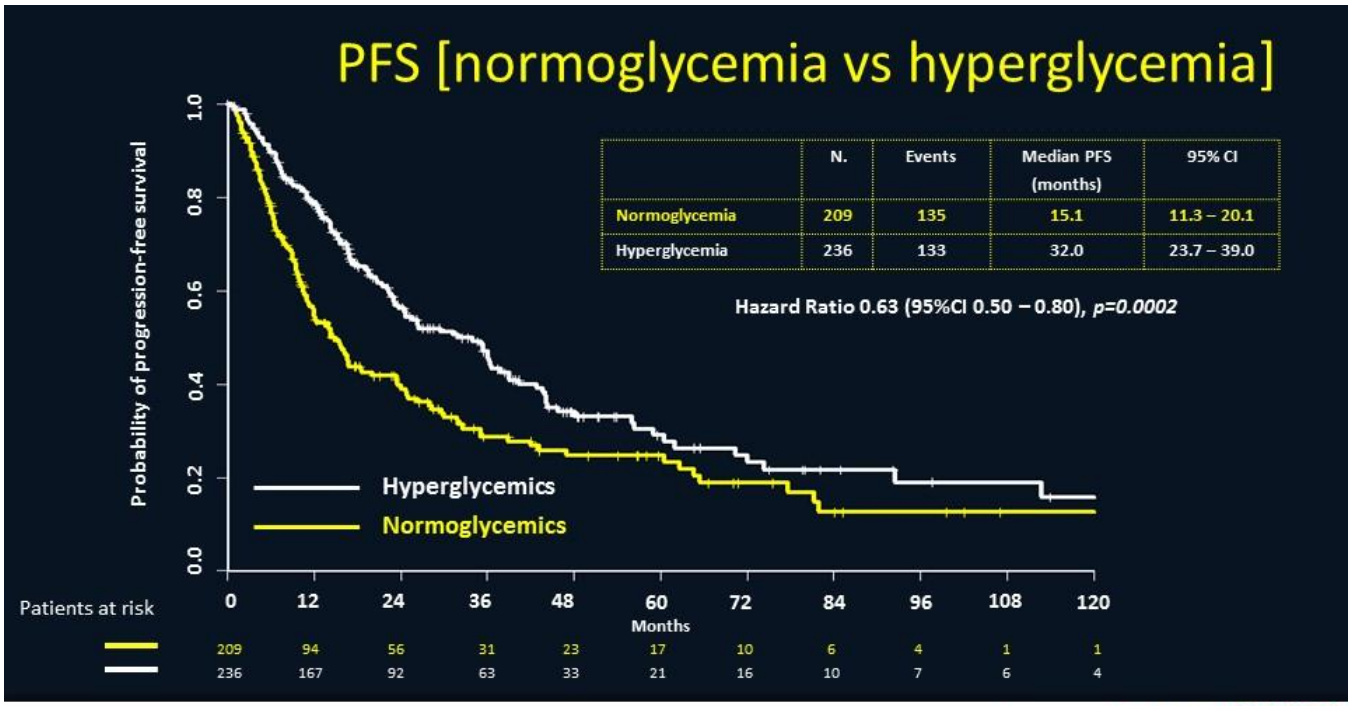
According to the current ESMO and ENETS guidelines, advanced carcinoid of the lung or thymus remains an area of high unmet medical need with few treatment options. Everolimus, which blocks the mTOR pathway, showed PFS benefit in patients with gastrointestinal/lung NET recently in the phase III RADIANT-4 study and the somatostatin analogue, pasireotide LAR, has also shown potential antitumour activity in NET studies. The investigators designed this phase II study entirely focused on patients with progressive advanced carcinoid of the lung or thymus and found clinical benefit and anti-tumour activity with everolimus and pasireotide LAR monotherapies that was greatest in the treatment arm that combined the two drugs. The combination of pasireotide LAR and everolimus had a statistically significant positive impact on the proportion of patients remaining progression free at 9 months. This combination warrants further study and looks promising to become a treatment option for patients with advanced lung and thymic carcinoids.

Risk of cancer progression in patients with diabetes and advanced pNETs significantly lowered by metformin treatment

Lead author Sara Pusceddu, Medical Oncology Department, Fondazione IRCCS - Istituto Nazionale dei Tumori in Milan, Italy presented findings from a multicentre, retrospective study that assessed the impact of hyperglycaemic versus normoglycaemic status on progression-free survival (PFS) in patients with pancreatic neuroendocrine tumours (pNETs), and evaluated the impact of concomitant metformin administered during everolimus and/or somatostatin analogue therapy. The investigators consulted the database of 24 Italian centres that included 445 patients who received everolimus and/or somatostatin analogue treatment for pNETs between 1999 and 2015. The patients' median age was 59 (range: 49 to 69) years and 53.5% of patients were male.

Of the patients with pNETs, 209 (46.7%) patients were normoglycaemic (non-diabetic) and 236 were hyperglycaemic (diabetic). Of the latter, 112 (25.2%) patients received metformin, 91 (20.4%) received insulin, and 33 (7.7%) patients were given dietetic counselling. The hazard ratio (HR) for risk of progression was calculated at 90% statistical power, with α error of 0.05 to detect risk of 0.67 in 445 hyperglycaemic versus normoglycaemic patients. The statistical power in the analysis of smaller subgroups of hyperglycaemic versus normoglycaemic patients on metformin and hyperglycaemic versus normoglycaemic on insulin was 77% to detect a hazard ratio [HR] of 0.67.

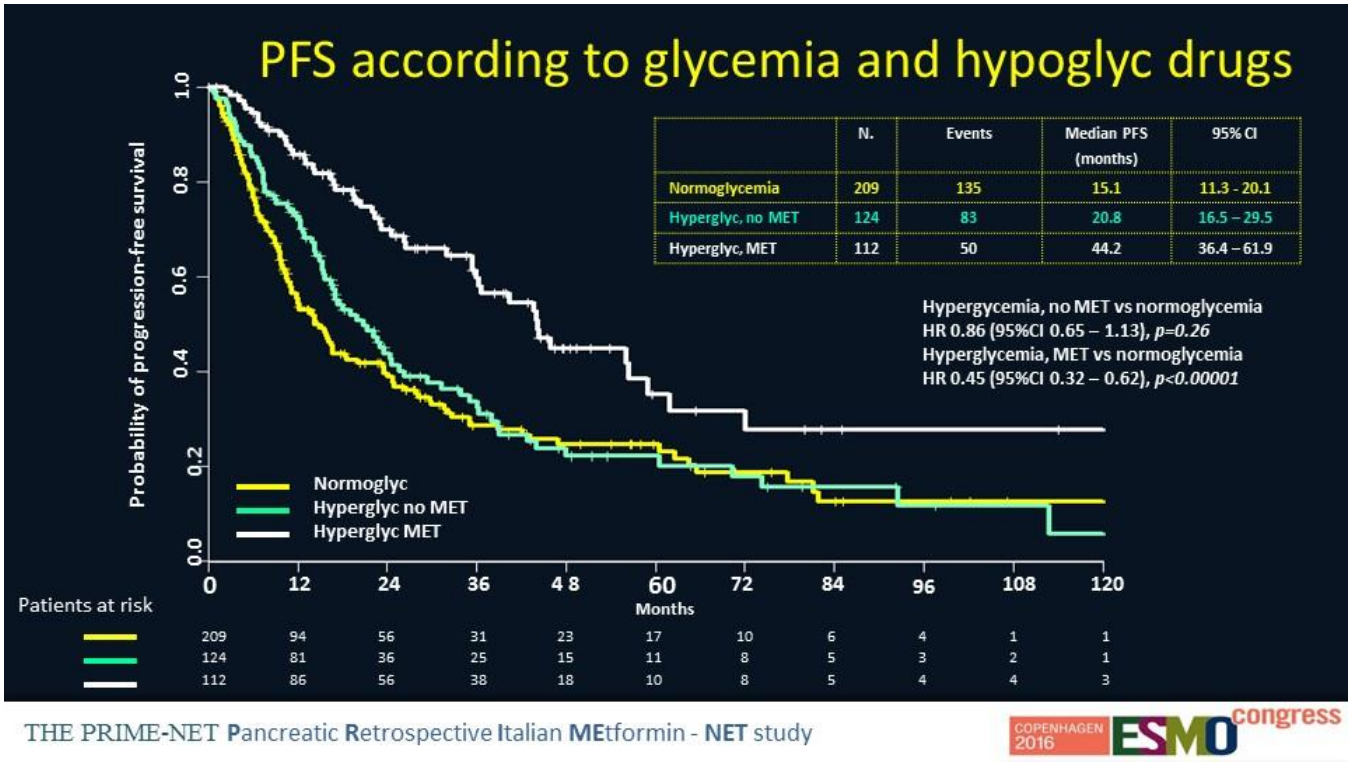
This analysis showed that patients with diabetes on metformin had longer PFS following treatment for pNETS than non-diabetic patients. In the overall population of patients treated for pNETs, median PFS was 23.4 months (95% confidence interval [CI] 19.1, 27.9). However, PFS was prolonged to 32 months in the subgroup of patients who had diabetes compared to just 15.1 months in normoglycaemic patients, HR 0.63; 95%CI 0.50, 0.80 (p = 0.0002).



*THE PRIME-NET **P**ancreatic **R**etrospective **I**talian **Me**tformin (**NET** study) - PFS (normoglycaemic vs hyperglycaemia).*

© Sara Pusceddu.

Patients receiving metformin for diabetes had the lowest risk of pNETs progression compared to non-diabetic patients. Subgroup analysis revealed that diabetic patients on insulin modulating therapy had a prognosis more similar to normoglycaemic patients, with a difference in PFS that was not statistically significant; the median PFS was 20.8 months (95% CI 15.6, 36.3) in patients receiving insulin versus normoglycaemic patients, HR 0.81; 95% CI 0.60, 1.1 (p = 0.18). However, diabetic patients on metformin showed the most prolonged PFS and lower risk of recurrence; PFS was 44.2 months (95% CI 36.4, 61.9) and the HR for progression versus normoglycaemic patients was 0.45; 95% CI 0.32, 0.62 (p< 0.0001).



*THE PRIME-NET **P**ancreatic **R**etrospective **I**talian **Me**tformin (**NET** study) - PFS according to glycaemia and hypoglyc drugs.*

© Sara Pusceddu.

Practice point and future research opportunities

Previous studies have suggested that patients with diabetes have an increased risk of developing cancer; however, metformin, the most widely used treatment in type 2 diabetes mellitus, has been associated with a decrease in cancer risk and has recently emerged as a potential anti-proliferation agent in cancer. Metformin acts by indirectly decreasing both glucose, insulin, and insulin-like growth factor 1 (IGF1) levels, and promoting both AMPK activation and mTOR inhibition by TSC1-2. This study has the limitations of any retrospective analysis but the findings from this large analysis were highly statistically significant and suggest that adding metformin to either everolimus or a somatostatin analogue may provide clinical benefit in patients with diabetes and advanced pNETs. These results warrant a prospective study to confirm these findings.

Genomic analysis of NETs facilitated by the NETwork! translational programme

Lead author Ben Lawrence, University of Auckland Faculty of Medical and Health Sciences in Auckland, New Zealand, presented the first findings of genetic analyses performed within NETwork! a clinical and ethical framework that was established to support, interpret, and return genomic analyses of neuroendocrine tumours (NETs). This framework includes a national New

Zealand registry of NETs that allows clinical annotation and is tethered to a NET-specific multidisciplinary meeting, which facilitates tissue collection. At ESMO 2016, findings were presented from genomic analyses of the first 61 pNETs done using this system. The investigators performed hybridisation capture DNA sequencing on 578 cancer-associated genes, which yielded greater than 750 times coverage, and microarray mRNA expression analysis was also done for all pancreatic NETs (pNETs). Additionally, whole genome sequencing, RNA sequencing, methylation, and microRNA (miRNA) expression analysis were done on 12 tumours. Clinical, pathological and genomic data were compared using a customised bioinformatic platform.

Dr. Lawrence and colleagues detected mutations in 75 cancer-associated genes, with 64 of these mutations being exclusive to individual tumours. Recurrent mutations were found at frequencies of 39% in MEN1 and 7% in ATRX genes. The driver genomic changes in pNETs were highly tumour-specific and included somatic mutations in the FANCA, APC, BRCA2, PTEN, EGFR, MDM4, MSH2 and VHL genes. The investigators also found mutations in ten additional genes that are not traditionally associated with cancer. A high rate of aneuploidy was observed in pNETs samples. Loss of heterozygosity (LOH) was detected in 18% of pNETs, which also showed an identical and previously undescribed pattern of LOH that involved the same ten whole chromosomes.

In depth analyses of the 12 tumours revealed gene expression profiles of immune activation. The investigators found that therapeutic choice as suggested using single biomarkers such as FANCA, and MSH2 could be further informed by multi-level genomics. An example was given of downstream activity negating a treatment decision, where the impact of a PTEN single nucleotide variation (SNV) was negated by LOH in downstream mTOR, thus reducing pathway activity. Another example was given of mTOR hypomethylation and expression changes being consistent with pathway activation. Lawrence *et al.* Abstract 418O

Practice point and future research opportunities

The NETwork! programme, facilitates largescale genomic analyses produced, which provide new insights into NET tumourigenesis. The endpoint is to enable rational and perhaps unexpected therapeutic choice to be applied in clinical trials. pNETs carry fewer genetic mutations compared with other tumour types, but demonstrate genomic alterations, including large-scale copy number, plus changes in epigenetic and gene expression. While mutations occur at a lower frequency in pNETs than other tumour types, the genomic variability uncovered in this study argues for multi-level sequencing of metastatic NETs, which may uncover potentially targetable alterations.

Landscape of pulmonary NETs defined by strategic use of whole-exome sequencing

I.G. Sullivan, Département d'Oncologie Médicale, Gustave Roussy, Villejuif, France,

and colleagues collected paired tumour/normal tissue fresh-frozen samples, including 35 typical carcinoid (TC), 4 atypical carcinoid (AC), and 9 large-cell neuroendocrine carcinoma (LCNEC) from consecutive patients attending 3 European centres between February, 2010 and November, 2013. The investigators selected specimens having more than 65% tumour cells on H&E staining by expert pathologists review, together with the paired sample for genomic DNA (gDNA) extraction. After normalization and quality control, gDNA was captured using in-solution enrichment methodology (Human All Exon V5+UTR–75 Mb, Agilent Technologies), and exome enriched libraries were sequenced on an Illumina HiSeq 2000 with a paired-end 2 x 100 bp protocol. Variants were identified using VarScan2 against the reference genome hg19 (GRCh37). After filtering based on frequency, variants were annotated using SnpEff and SnpSift with dbSNP and dbNSFP.

Typical and atypical carcinoid samples were from females in 59% of cases whereas 89% of LCNEC samples were from males; the patients overall were aged from 18 to 83 years. The samples were from 26 (54%) patients with stage I, 16 (24%) with stage II, 3 (6%) with stage III, and 3 (6%) patients with stage IV disease.

On average, 11.6 Gb of sequence were produced per sample, aiming a mean coverage of 72 X. A median of 277 (range: 10 to 8470) somatic variants per sample was observed, which may potentially represent an actionable target. Preliminary analysis revealed several somatic variants in histone modifiers, including 9 MEN1, 6 EZH2, and 5 HDAC5. Variants in genes involving the SWI/SNF complex, including ARID, BCL-2 and SMARCA were also found and several variants were observed in the PIK3 family of the mTOR pathway. Although, none of the detected alterations were enriched in any pulmonary NET subtype, 6 TP53 and 3 RB1 variants were observed exclusively in LCNEC samples. Sullivan *et al.* Abstract 419O

Practice point and future research opportunities

Treatment of pulmonary NETs remains a clinical challenge making the identification of targetable molecular alterations a priority. This whole exome sequencing study provides insight into the genomic landscape of pulmonary NETs that may open up offering future opportunities for precision medicine in these patients.

Comprehensive genomic profiling reveals paediatric, adolescent and young adult thyroid carcinomas harbour frequent and diverse therapeutically targetable genomic alterations

Lead author Pierre Vanden Borre, Biomedical Informatics, Foundation Medicine, Inc., Cambridge, USA, presented findings from an analysis using hybrid-capture based comprehensive genomic profiling (CGP) on 58 paediatric and young adult (PAYA) thyroid carcinomas. Overall, 64% of patients were female and the median age was 39 years or younger; the median age was 26 (range 7 to 39) years of 41 patients with papillary thyroid carcinoma (PTC), 33 years (range: 25 to 33) years in 3 patients with anaplastic thyroid carcinoma (ATC), and 14 patients with medullary thyroid carcinoma (MTC) had a median age of 33 years, (range: 15-39).

Genomic alterations occurred at a high frequency and were detected in 93% of samples, with a mean of 1.4 genomic alterations per case. Genomic alterations that were clinically relevant, defined as being associated with at least one actively recruiting clinical trial or an FDA-approved therapy, were identified in nearly all (91%) cases. BRAF V600E was present in 46% of PTCs and in 33% of ATCs. PTC samples also harboured oncogenic fusions in 37% of cases, which were also present in and 33% of ATC cases. Fusions in RET, NTRK1, and NTRK3 had been previously observed in PAYA thyroid carcinoma; this analysis revealed 3 ALK fusions (EML4-ALK, STRN-ALK, and GTF2IRD1-ALK) in patients with PTC. RET mutation occurred in 93% of young adult patients with MTC, including the predominant RET M918T mutation, and 3 insertion/deletions in exons 6 and 11.

Vandetanib was given to 2 patients with MTC who harboured in-frame deletions in RET exons 6 and 11 that resulted in clinical benefit in both patients. Vanden Borre *et al.* Abstract 427PD

Practice point and future research opportunities

Diverse targetable genomic alterations are present at a high incidence in paediatric and young adult patients with thyroid carcinoma; of these, the majority of papillary thyroid cases harboured either activating kinase mutations or rearrangements, including three cases with ALK fusions. Findings from this genomic profiling data, taken together with clinical observations suggest that young patients with advanced thyroid carcinoma can often benefit from comprehensive genomic profiling to identify targetable genomic alterations. Additionally, several alterations were identified that offered the possibility for use of existing targeted therapies, including two cases where treatment was initiated and successful.

GASTROINTESTINAL TUMOURS - Colorectal

Greater tumour downstaging with a 12 versus 6-week interval between interventions in rectal cancer

Jessica Evans, Colorectal Surgery, Royal Marsden Hospital NHS Foundation Trust, London, UK urged clinicians to employ a longer waiting interval from the end of preoperative chemoradiotherapy to surgery. A 12-week interval was found to increase the rate of pathological complete response (pCR) and to yield a higher proportion of patients achieving tumour downstaging, as compared to a 6-week interval in patients with locally advanced rectal cancer, according to findings from this prospective, randomised, multicentre trial.

The trial was designed to determine whether a 6- or 12-week interval between neoadjuvant chemoradiotherapy and surgery is optimal in patients with locally advanced rectal cancer to allow greater rectal cancer downstaging and tumour regression, which could improve the rates of sphincter preservation and achieve improved local control. This study enrolled 237 patients with locally advanced rectal cancer to receive chemoradiotherapy followed by surgery. Following chemoradiotherapy, 122 patients were randomised to a cohort with a planned 6-week interval and 115 patients were randomised to another cohort with a 12-week interval between chemoradiotherapy and surgery.

Differences were observed between the two cohorts in the proportion of patients achieving downstaging of their tumours and in the pCR rates. A greater proportion (58%) of patients in 12-week interval cohort had tumour downstaging compared with 43% of patients in the 6-week interval cohort ($p = 0.019$). An improved rate of pCR was also observed with a longer interval; the pCR rate was 20% in the 12-week versus 9% for the 6-week cohort ($p < 0.05$). Additionally, more patients in the 12-week interval cohort achieved magnetic resonance tumour regression grade of 1 or 2 (mrTRG 1-2 rate); the mrTRG 1-2 rate in the 12-week arm was 52% versus 34% in the 6-week arm ($p < 0.05$). Evans *et al.* Abstract 452O

Practice point and future research opportunities

Findings from this randomised study indicate that patients may benefit from a longer interval between chemoradiotherapy and subsequent surgery that ultimately could afford greater sphincter preservation and control of local disease recurrence. A longer interval of 12 rather than 6 weeks after chemoradiotherapy prior to surgery demonstrated significantly greater tumour downstaging, improved pCR rates, and greater mrTRG. Since obtaining a pCR after the neoadjuvant treatment is an accepted surrogate measure of disease-free survival, undertaking surgery before maximal regression may be disadvantageous in patients with locally advanced rectal cancer. The authors recommend adopting a change in the standard from undertaking surgery at 6 to 8 weeks to 12 to 14 weeks. These findings support this recommendation but this change can only be safely undertaken if MRI evaluation of response or progression is still made at 4 to 6 weeks.

Long-term results show scheduled use of CEA and CT follow-up detects more recurrence of colorectal cancer than minimal follow-up

Lead author Sian Pugh, University Surgery, University of Southampton, Southampton, UK presented findings from the FACS trial, which evaluated the utility of adding computed tomography (CT) imaging, measurement of carcinoembryonic antigen (CEA), or both for follow-up of patients with undergoing curative R0 resection, stages I-III for colorectal cancer. An interim analysis showed that all intensive strategies identified more recurrences that could be surgically treated with curative intent compared to minimum follow-up; however, no advantage was seen in using both CT and CEA. At ESMO 2016, Dr. Pugh reported the results from the mature analysis, including overall survival (OS) up to 12 years post randomisation comparing the intensive modes of follow-up to minimum follow-up. The FACS study randomised 1202 participants to regular CEA measurement, regular CT imaging of the chest, abdomen, and pelvis, combined CEA plus CT, or to minimum follow-up comprising symptomatic follow-up with/without single CT. The primary endpoint was surgical treatment of recurrence with curative intent. The actual follow-up was for 5 years; thereafter OS monitoring continued using registry data for a median follow-up of 8.7 years.

Long-term surveillance revealed more recurrences treatable with curative intent were identified with intensive follow-up of 68 (7.5%) recurrences in the combined intensive cohort of 901 patients versus 8 (2.7%) recurrences in the minimal cohort of 301 patients ($p = 0.003$). Although no statistically significant difference in OS between groups was observed ($p = 0.45$), numerically more patients with recurrence were still alive in intensive groups; 43 (4.8%) patients in the intensive versus 7 (2.3%) in the minimal cohort ($p = 0.07$). An OS benefit in patients with recurrence was seen only in patients with a left colonic tumour, where median OS of 4.4 years with intensive versus 3.1 years with minimal follow-up ($p = 0.03$).

Analysis by site of primary tumour revealed a similar proportion of curatively treatable recurrences in patients with rectal tumours irrespective of follow-up; 27 (9.8%) versus 6 (6.9%) patients were detected in the intensive versus minimal cohorts, respectively ($p = 0.41$). However, patients with a colonic tumour benefited more from intensive follow-up wherein treatable recurrence was more commonly detected: 24 recurrences were detected in the left colon (7.3%) versus 1 (0.9%) in the minimal arm ($p = 0.01$); similarly, intensive follow-up detected 14 (5%) recurrences in the right colon versus none by minimal follow-up ($p = 0.02$). ISRCTN 41458548 Pugh *et al.* Abstract 453O

Practice point and future research opportunities

Intensive follow-up entailing CT, measurement of CEA, or both increased the detection of treatable recurrences over minimal follow-up, although further analysis suggested this was only the case for colonic tumours. Longer follow-up revealed a survival advantage with intensive versus minimal follow-up, but only patients with recurrence from a left colonic tumour, which underscores the heterogeneous biology of colorectal cancer.

Nintedanib in refractory mCRC

Lead author Eric Van Cutsem, head of Digestive Oncology at University Hospitals in Leuven, Belgium presented results on behalf of colleagues from the LUME-colon 1 study, which was the first phase III trial of nintedanib in colorectal cancer. The trial enrolled 768 patients with metastatic colorectal cancer (mCRC) in good general condition, defined as performance status 0 and 1, and with good organ function, who were refractory to standard therapies including oxaliplatin, irinotecan, fluoropyrimidines, anti-VEGF, and anti-EGFR (in patients with RAS wild-type tumours). The patients were randomised 1:1 to nintedanib or placebo, each plus best supportive care. The co-primary endpoints were progression-free survival (PFS) and overall survival (OS).

Median PFS with nintedanib was 1.5 month compared to 1.4 month with placebo, hazard ratio 0.58; 95% confidence interval [CI] 0.49, 0.69 ($p<0.0001$). Significantly improved disease control was seen with nintedanib of 26% compared to 11% with placebo, odds ratio 2.96; 95% CI 2.00, 4.4 ($p < 0.0001$). However, no difference in OS was observed between the two groups; median OS was 6.4 months versus 6.1 months with nintedanib versus placebo, respectively. Nintedanib was well-tolerated. Serious adverse events occurred in 39% of patients on nintedanib and in 35% of patients on placebo. Treatment was discontinued in 14% of patients in the nintedanib due to adverse events, compared to 11% in the placebo group.

Professor Van Custom noted that patients on placebo survived longer than expected and speculated that treatments taken after the trial ended may have contributed to this finding, since the follow-up continued after the trial finished until the patient died. Additional analyses of molecular markers and the nintedanib response in subtypes of colorectal cancer are ongoing to identify patients that could benefit from nintedanib. NCT02149108. Van Cutsem *et al.* Abstract LBA20_PR

Practice point and future research opportunities

Colorectal cancer is a frequently occurring disease and a large proportion of patients develop metastases. There is a need to find new therapies for this large group of patients, many of whom initially respond to several different lines of treatment and then stop. Nintedanib is a multiple tyrosine kinase inhibitor that has shown to control angiogenic activity, which is necessary to support tumour growth**.**

This trial evaluated nintedanib in patients with metastatic colorectal cancer who were refractory to all available treatments including chemotherapy and biological therapies. Nintedanib gave a significant increase in PFS and disease control but patients receiving nintedanib did not live longer. Nintedanib delays disease progression and increases the rate of stable disease but these gains were lost when it came to OS, in contrast to regorafenib and trifluridine/tipiracil which improve both PFS and OS in these patients. The disparity may have arisen because patients who progressed in the LUME-colon 1 trial received more salvage treatments than in the earlier trials, which is supported by the relatively long OS in patients receiving placebo. More data are needed to explain the findings and understand how strong the benefit of nintedanib really is.

Bevacizumab plus metronomic chemotherapy yields no added benefit over sole bevacizumab as maintenance following FOLFOXIRI/bevacizumab in mCRC

Alfredo Falcone, U.O. Oncologia Medica 2 Universitaria, Azienda Ospedaliera Universitaria S. Chiara, Pisa, Italy headed a team of investigators from Italian institutions in conducting the phase II MOMA multicentric study. MOMA compared two maintenance therapies in patients with unresectable metastatic colorectal cancer (mCRC). After receiving up to 8 cycles of FOLFOXIRI plus bevacizumab, randomised patients received either bevacizumab (arm A; n=117), or bevacizumab plus metronomic chemotherapy consisting of capecitabine 500 mg/tid and cyclophosphamide 50 mg/die per os (arm B; n=115) until disease progression. The primary endpoint was progression-free survival (PFS) which required 173 events.

Patients in arms A and B had a median age of 61 versus 62 years, presence of synchronous metastases in 81% versus 83%, liver-only disease in 27% versus 35%, and right-sided primary tumour in 32% versus 42% patients, respectively. RAS mutations were present in 66% versus 63%, BRAF mutation in 7% versus 10%, and RAS/BRAF was wild-type in 18% versus 14% patients in arms A and B, respectively. RAS or BRAF was not evaluable 9% of arm A versus 13% of arm B patients and 85% of patients in each arm were ECOG performance status 0.

At a median follow up of 25.7 months, 188 patients overall had progressive disease. No significant difference in PFS was demonstrated between arms; median PFS was 9.5 months in arm A compared to 10.6 months in arm B, hazard ratio 0.99 (p = 0.926). The response rate with induction FOLFOXIRI plus bevacizumab was 63% overall, and 68% versus 58% in arm A versus arm B, respectively.

The subgroup of 72 patients with metastasis limited to the liver demonstrated a secondary resection rate of 49% overall, and 53% versus 45% in arm A versus arm B, respectively.

Grade 3/4 adverse events of neutropenia were reported in 51% of patients overall, febrile neutropenia in 11%, and diarrhoea in 13% of patients during induction, whereas during maintenance, hypertension was reported in 4.6% versus 2.6%, and venous thrombosis in 2% versus 3% of patients in arms A and B, respectively. Hand-foot syndrome was reported by 8% of patients in arm B only. NCT02271464. Falcone *et al.* Abstract LBA21

Practice point and future research opportunities

Although a common treatment strategy in mCRC is to alternate induction and maintenance phases, the optimal duration of induction and the optimal maintenance remain unresolved. In the MOMA study, metronomic chemotherapy added to bevacizumab showed no additional benefit over bevacizumab as maintenance. These findings show a response rate that confirms the activity of induction FOLFOXIRI plus bevacizumab in a patient population with a high prevalence of RAS and BRAF mutant tumours.

Napabucasin (BBI608) trial in advanced colorectal cancer halted early after futility analysis

Dereck J. Jonker, Department of Medicine, Division of Medical Oncology, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada Presented results from the phase III study that enrolled 282 patients with advanced colorectal cancer (aCRC) who had failed all available standard therapies. The patients' median age was 64 (range: 32 to 85) years, and 65% of patients were male, and ECOG perfomance status was 0 or 1 in 28% and 72% of patients, respectively. The majority, 98%, of patients had received >4 prior regimens, including 89% of patients receiving prior anti-VEGF. Fifty-two percent of patients had KRAS wild-type tumours. The trial randomised 138 patients to napabucasin at 480 mg orally and 144 patients to placebo. Patients were treated from April, 2013 to May 2014 when the trial was unblinded, accrual closed, and the protocol treatment was halted after the futility analysis of the disease control rate in the first 96 patients. The pre-defined Minimum Effective Treatment in patients who received ≥50% of the total daily dose for 6.4 weeks or more was 6.6 months with napabucasin versus 5.8 months with placebo, hazard ratio [HR] 0.88 (p = 0.5). The primary endpoint, overall survival (OS), was not met; median OS was 4.4 months with napabucasin versus 4.8 months with placebo hazard ratio [HR] 1.13 (p = 0.34).

Napabucasin did demonstrate activity in a subgroup of 55 patients that were positive for STAT3 expression, as identified in a pre-specified biomarker analyses that included pSTAT3 positivity by immunohistochemistry in archival tissue based on nuclear staining of cancer cells >5% and stroma ≥2+. Median OS in this group was significantly prolonged with napabucasin to 5.1 months versus 3.0 months with placebo, HR 0.24; 95% confidence interval [CI] 0.12, 0.51 (p = 0.0002).

Adverse events (AEs) were more common with napabucasin than placebo. The most common grade 3 AEs with napabucasin were diarrhoea, occurring in 88% of patients, nausea in 63%, and fatigue in 65% of patients. Anorexia occurred in 56% of patients, and grade 3 diarrhoea occurred in 57% of patients. NCT01830621. Jonker *et al.* Abstract 454O

Practice point and future research opportunities

Despite early-phase research showing antitumour activity for napabucasin, a cancer stemness inhibiting agent that targets STAT3, no significant difference in OS, was seen between napabucasin and placebo in the intention to treat analysis in unselected patients. While pSTAT3 positivity was a poor prognostic factor in untreated patients, napabucasin treatment in patients with positive pSTAT3 significantly improved OS.

Napabucasin has demonstrated benefit when used in combination with weekly paclitaxel, resulting in the FDA granting orphan drug designation to napabucasin as a treatment for patients with gastric or gastroesophageal junction cancer. In addition to gastric cancer, napabucasin is also being explored as a potential treatment for patients with pancreatic cancer, ovarian cancer, triple-negative breast cancer, and colorectal cancer.

Integrated biomarker analysis done for combination dabrafenib / trametinib / panitumumab therapy in BRAF V600E mutation positive mCRC

Lead author Ryan B Corcoran, Translational Research Director for the Gastrointestinal Cancer Center at Massachusetts General Hospital, Boston, USA and a Damon Runyon Clinical Investigator, presented findings on behalf of colleagues from a study testing whether combined inhibition of the EGFR pathway with panitumumab, and dual inhibition of the MAPK pathway could improve clinical benefit in BRAF mutated metastatic colorectal cancer (mCRC). This study evaluated the efficacy and safety of panitumumab plus MAPK pathway inhibitors dabrafenib or trametinib, and in triple combination with both. The trial enrolled 134 patients with BRAF mutated mCRC who were randomised to receive panitumumab plus dabrafenib (n=20), panitumumab plus trametinib (n=31), or a triple combination of panitumumab, dabrafenib and trametinib (n=83). Each agent in the combination could be administered at a dose of up to the full monotherapy dose. The majority of study participants, 120 patients, had received prior chemotherapy for mCRC and 14 patients were treatment-naive. The trial included integrated biomarker analyses. Tumour biopsies that were taken prior to and during treatment were evaluated by immunohistochemistry for phosphorylated ERK (pERK). Serial circulating tumour DNA (ctDNA) samples were obtained and profiled for mutations in the BRAF, KRAS, NRAS, and PIK3CA genes.

The highest response was observed with the triple combination treatment. Patients in the dabrafenib/panitumumab arm showed a confirmed complete response and partial response (CR/PR) rate of 10%, and 80% of patients achieved stable disease (SD). With trametinib/panitumumab no patients attained CR/PR but 53% showed SD. However, the two agents combined with panitumumab yielded an 18% CR/PR rate and 67% of patients showed SD. Median PFS for combined dabrafenib/trametinib/panitumumab was not yet been reached compared with median PFS of 3.4 and 2.8 months demonstrated with dabrafenib/panitumumab and trametinib/panitumumab, respectively. The triple combination showed acceptable toxicity, and the most common adverse events were dermatitis acneiform, diarrhoea, fatigue, nausea and rash.

The integrated biomarker analysis detected changes in different genes with response and upon disease progression. Immunohistochemistry done in biopsies revealed a reduction in pERK in on-treatment versus pre-treatment biopsies. The median pERK reductions were 23% for dabrafenib/panitumumab, 50% for trametinib/panitumumab, and 54% for the triple combination. Serial ctDNA analysis also showed reductions in the BRAF V600E mutant fraction of more than 70% as early as week 4 of treatment in 12 of 14 (86%) patients receiving dabrafenib/trametinib/panitumumab. This finding corresponds with the PR achieved by 6 of these 12 patients by week 6. Conversely, ctDNA analysis also demonstrated increased BRAF V600E mutant fraction in 10 patients upon progression.

Other mutations that were not present at baseline were detected in ctDNA upon progression. Of the 12 patients showing a best response of CR/PR or SD, 7 (58%) patients had RAS mutations

in ctDNA upon progression that were not detectable at baseline; 3 of these patients developed multiple RAS mutations. In addition, BRAF V600E and RAS mutations were co-expressed in 2 patients at baseline. NCT01750918. Corcoran *et al.* Abstract 455O

Practice point and future research opportunities

Dabrafenib and trametinib have demonstrated activity and have been approved for BRAF-V600E-mutated melanoma, for use either as single agents or in combination; both drugs block the MAPK pathway, dabrafenib by inhibiting BRAF and trametinib by inhibiting MEK1 and MEK2. BRAF-V600E mutations have been reported in 5% to 10% of mCRC cases; however, BRAF and MEK inhibiting monotherapies have been shown to have little activity in mCRC, where the presence of a BRAF V600E mutation often signals a poorer prognosis.

This study demonstrated that the response in BRAF V600 mutated mCRC could be improved by blocking the EGFR pathway and dual blocking of the MAPK pathway. Patients with mCRC whose tumours harboured BRAF V600E mutation that received triple therapy comprising dabrafenib, trametinib, and panitumumab showed an improved best overall response and prolonged PFS compared to a double blocking combination of panitumumab plus either dabrafenib or trametinib. The demonstrated efficacy taken together with acceptable toxicity demonstrate that this triple combination may be a possible treatment option in mCRC.

The integrated biomarker analysis by immunohistochemistry provided evidence of downstream target inhibition. The ctDNA data suggested that changes in BRAF V600E mutation frequency may serve as a biomarker of response, and could be used to monitor treatment response by decreased pERK and disease progression, which was reflected in an increase of BRAF V600 mutation fraction. The presence of emergent RAS mutations may represent potential mechanisms of resistance to combination treatment.

Results of the first cohort of patients screened within the new EORTC SPECTAcolor platform for patients with colorectal cancer

Gunnar Folprecht, Medical Department I, University Hospital Carl Gustav Carus in Dresden, Germany, presented findings on behalf of colleagues from the first cohort screened in conjunction with SPECTAcolor (Screening Platform for Efficient Clinical Trial Access in advanced colorectal cancer), which was initiated by the European Organisation for Research and Treatment of Cancer (EORTC) as the first prospective, fully annotated tumour sample biobank and biomarker analysis platform for genetic profiling of patients with advanced colorectal cancer. The aim is to facilitate patient-access to a clinical trial for treatment with a targeted agent. Since the inception in 2013, this biobank has enrolled more than 900 patients from 32 clinical centres in 11 European countries and anticipates enrolling at least this many patients yearly in the upcoming years.

Dr. Folprecht reported findings from a cohort of 389 patients with CRC who underwent screening using a large next generation sequencing (NGS) panel comprising 328 cancer genes. All

analyses were performed according to Good Clinical Laboratory Practice (GCLP) Standards. Limited gene fusions were assessed in a subset of samples and genetic events were detected by an ISO 13485-accredited analysis pipeline.

Using immunohistochemistry or fragment length analysis, the investigators determined that 370 of the 389 (95.2%) patients overall were microsatellite stable (MSS) and 19 (4.8%) patients were highly microsatellite instable (MSI-H). Both MSS and MSI-H tumours were found to contain a median of 3 (range: 0 to 16) driver mutations and a median of 8 (range: 3 to 16) potential driver mutations. Among patients with MSS colorectal cancer, 77.8% had mutations in APC, 72.2% in TP53, and 47.8% of patients showed KRAS mutation. Mutated PIK3CA, FBXW7, and BRAF were present in 17.6%, 11.1% and 10.5% of patients. Mutations in the SOX9, SMAD4, ARD1A, and NRAS were present in less than 10% of patients.

More patients with MSI-H tumours that showed TP53 mutations (52.6%), PIK3CA (47.4%), and 42.1% had KRAS mutation. FBXW7 and BRAF mutations were each present in 36.8% of patients and APC and SOX9 were each mutated in 21.1% of patients. No mutations in SMAD4, ARD1A, and NRAS were detected in MSI-H patients.

Tumour localisation of APC and TP53 was more often on the left versus right side, 80.8% versus 73.6%, and 76.5% versus 62.3%, respectively, whereas KRAS and PIK3CA occurred more often on the right; KRAS location was 45.5% versus 53.8%, and PIK3CA was 14.1% versus 25.5%, left versus right, respectively. The prevalence of BRAF mutated tumours was predominately right side: 5.1% left versus 22.6% right ($p < 0.0001$).

Additionally, the investigators detected BRCA2 mutation in 1.6% of patients, located left at 0.8% versus 3.8% right, and in 5.3% of MSI-H tumours. A total of 1.9% of patients showed ERBB2 mutation, which was found twice as often in left sided tumours; left 2.0% versus 1.0% right. Other potentially actionable targets included ERBB2 amplification in 2.5% of patients, FGFR1/2/3 amplification in 3.5%, and TSC1 mutation in 16% of patients with MSI-H tumours. Single ALK and ROS fusions were also observed. NCT01723969. Forprecht *et al.* Abstract 458O

Practice point and future research opportunities

Results of gene panel sequencing from the first cohort of patients with advanced colorectal cancer participating in SPECTAcolor, a large European screening platform revealed new, potentially actionable genetic alterations in these patients, many of whom were now eligible to enter a clinical trial of targeted therapies. New therapeutic targets were detected by gene panel sequencing in approximately 10% of patients with colorectal cancer participating in SPECTAcolor. These first results show that SPECTAcolor is an effective platform for screening patients with colorectal cancer to identify rare but potentially actionable genomic targets; Patients participating in SPECTAcolor will have better access to targeted therapy.

ERBB2 alterations emerged from a FOLFOX based adjuvant trial as a potential new prognostic biomarker in stage III colon cancer

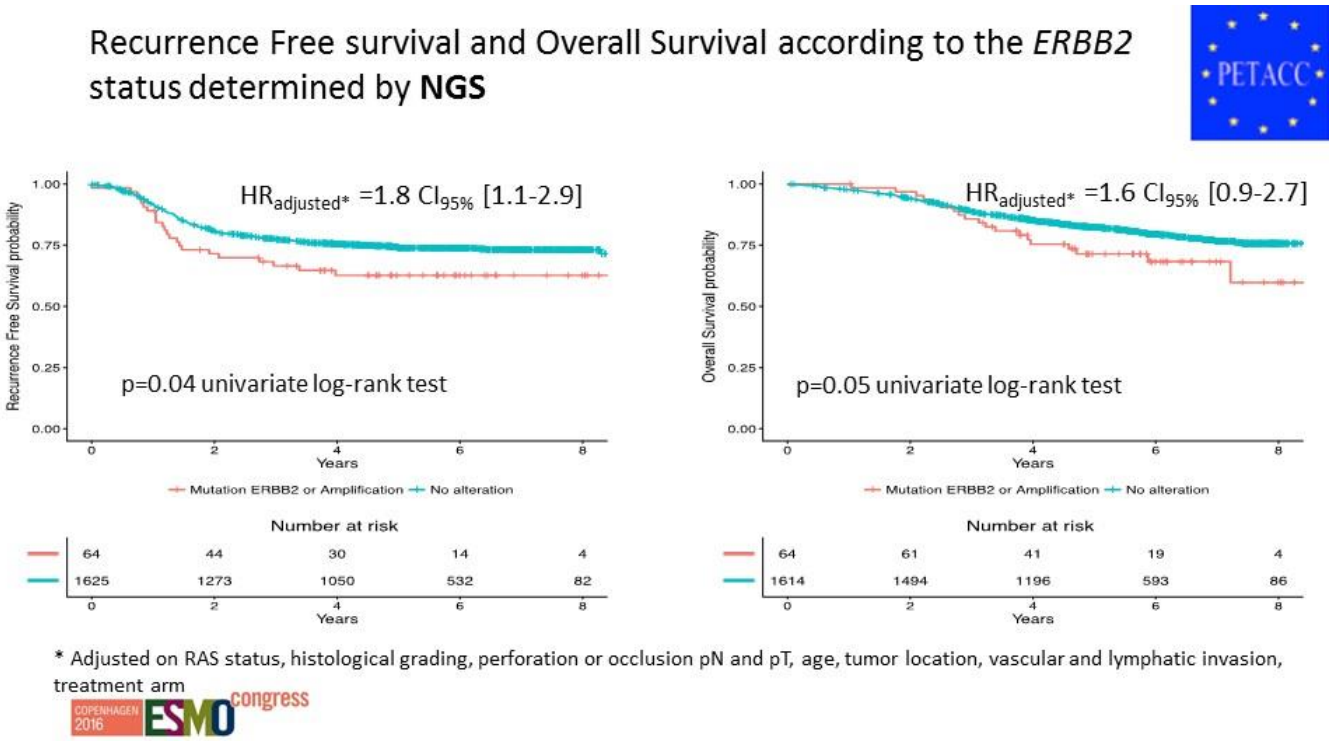
Pierre Laurent-Puig, Department of Biology, Hôpital Européen Georges Pompidou, INSERM UMR-S1147, Paris Descartes University in Paris, France, explained that ERBB2 amplifications have recently been shown to be a targetable alteration in metastatic colorectal cancer (mCRC). Lending further impetus to this study was the response seen in the HERACLES trial with dual-targeted therapy comprising trastuzumab and lapatinib in patients with HER2-positive mCRC. Prof. Laurent-Puig emphasised that defining the occurrence and prognostic role of ERBB2 alterations in stage III colon cancer could lead to additional adjuvant strategies, which are sorely needed in colon cancer.

The PETACC8 trial enrolled 2559 patients with resected, histologically proven stage III colon adenocarcinoma and 2043 patients signed the informed consent for the translational research programme. Of these,1795 patients had tissue samples for screening by next generation sequencing (NGS), and 1804 patients had samples for immunochemistry and FISH analyses.

The investigators searched for amplification of the ERBB2 gene and for mutation in exons 19 to 21 using the colon/lung cancer panel V2 and an algorithm that had been previously validated. All samples were screened for ERBB2 staining with polyclonal antibody HER2 clone 4B5 from Ventana Roche and by FISH using kit zytolight SPEC ERBB2/CEN17 dual colour.

By these methods, ERBB2 alterations were detected in 64 (3.8%) patients; of these, 17 (1%) samples contained ERBB2 mutations. The most frequently detected mutations were p.V842I in 5 patients, and 3 samples each harboured p.V777L and p.L755S mutations. Neither a significant association with RAS or BRAF mutations nor mutual exclusivity was determined. ERBB2 amplification was detected in 49 (2.9%) patient samples by NGS that were confirmed in 28 cases by FISH.

On univariate analysis, ERBB2 alterations signalled a poorer prognosis and were associated with both shorter time to recurrence (TTR), hazard ratio [HR] 1.55; 95% confidence interval [CI] 1.02, 2.36 (p = 0.04), and shorter overall survival, HR 1.57; 95% CI 0.99, 2.5 (p = 0.05). The prognostic value in TTR remained following adjustments for confounders, including treatment, the presence of RAS mutation, histological grade, tumour location, pT and pN status, and the presence of bowel obstruction or perforation, and venous or lymphatic embolism. EudraCT number 2005-003463-23. Laurent-Puig *et al.* Abstract 459O



Recurrence-free survival and overall survival according to the ERBB2 status determined by next-generation sequencing.

Practice point and future research opportunities

Findings from the adjuvant PETACC8 trial and results of a large-scale molecular analysis suggest that ERBB2 gene alterations may be prognostic of poorer outcome in stage III colon cancer. Although ERBB2 alterations, including mutations and amplification, occur at a low frequency in colon cancer, their presence associated with a markedly poorer prognosis, making both screening for ERBB2 alterations and the testing of anti-ERBB2 therapies a consideration in the adjuvant colon cancer setting. ERBB2 alteration occurs in approximately 4% of patients with stage III colon cancer, and associated with decreased time to recurrence and shorter overall survival. Since ERBB2 alteration signals a poor prognosis, the use of anti-ERBB2 therapies in the adjuvant setting is supported for testing in a clinical trial context. ERBB2 has emerged as a new prognostic, albeit rare, biomarker in stage III colon cancer.

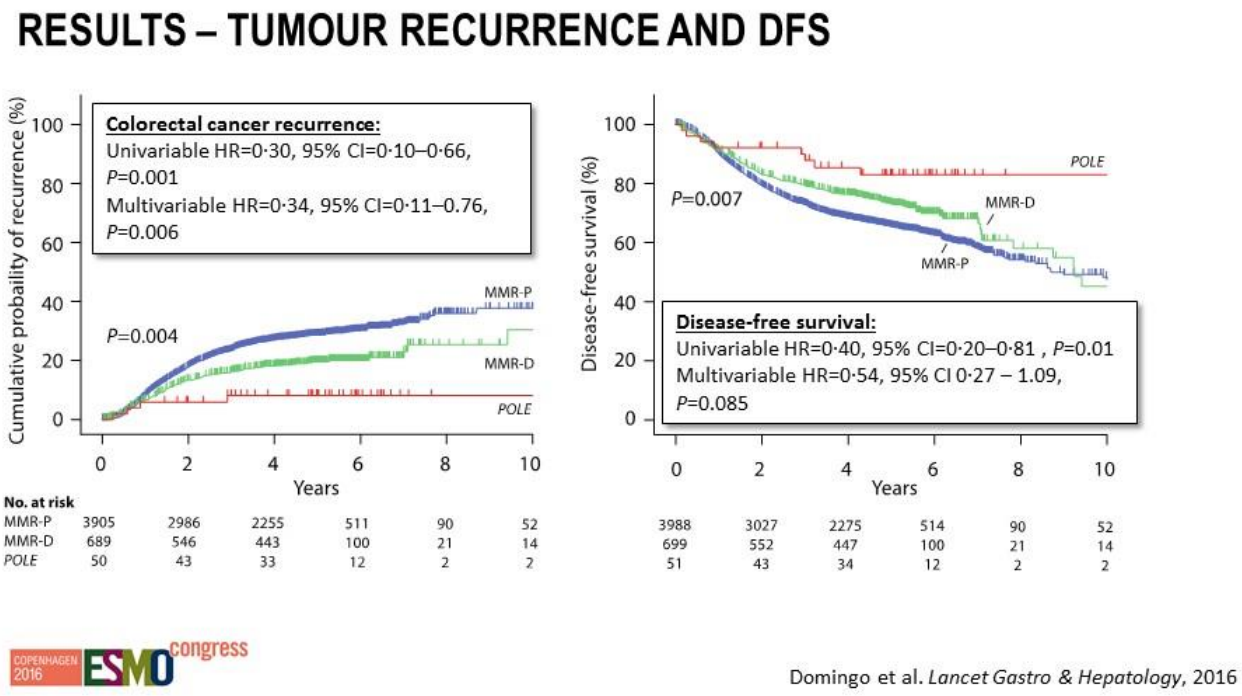
Mutations in the *POLE* proofreading domain identify a subset of colorectal cancers that have enhanced immunogenicity and an excellent prognosis

Mark Andrew Glaire, of the Oxford Centre for Cancer Gene Research, Wellcome Trust Centre

for Human Genetics, University of Oxford, Oxford, UK underscored the importance of using biomarkers, even those occurring at low frequencies, in defining distinct tumour subgroups. He explained that exceptionally mutated (ultramutated) tumours resulting from mutations that impair DNA polymerase epsilon (*POLE)* proofreading function confer enhanced immunogenicity and excellent prognosis in the approximately 10% of endometrial cancers in which they are found; however, their effect in colorectal cancer had not yet been defined.

In order to determine the clinical relevance of *POLE* mutations in colorectal cancer, Dr. Glaire and colleagues performed Cox regression analysis on pooled data from more than 4500 patients participating in 3 clinical trials (VICTOR, QUASAR2 and PETACC-3) and multiple patient cohorts (LUMC, Oslo, Bern, AMC-AJCC-II, EPICOLON, and TCGA), and investigated the association between *POLE* mutations and prognosis in stage II/III disease. They detected *POLE* mutations in just 66 of 6,448 (1.0%) colorectal cancer samples. Although uncommon, *POLE* mutations were significantly associated with several patient and tumour factors, including young age, male sex, right-sided location, early disease stage, and absence of mismatch repair deficiency (MMR-D; $p \leq 0.003$ for all associations).

Importantly, multivariable analysis revealed a statistically significant association between *POLE* mutation and a greatly reduced risk of disease recurrence: hazard ratio [HR] 0.34; 95% confidence interval [CI] 0.11, 0.76 ($p = 0.006$). This reduced risk was particularly strong in stage II disease, HR 0.22; 95%CI 0.02, 0.78 ($p = 0.014$). This reduction in relative risk was greater than that associated with MMR-D (HR 0.72; 95%CI 0.60, 0.87), an accepted biomarker of favourable prognosis in this setting.



COPENHAGEN 2016 ESMO congress

Domingo et al. *Lancet Gastro & Hepatology*, 2016

Results – Tumour recurrence and disease-free survival.

These results may be explained by increased immune activity in *POLE*-mutant tumours including increased $CD8^+$ lymphocyte infiltration, expression of cytotoxic T cell markers, and effector cytokines, which was similar to that observed MMR-D cancers, well-recognised to be immunogenic. Glaire *et al.* Abstract 460O

Practice point and future research opportunities

POLE proofreading domain mutations, which indicate enhanced immunogenicity and improved prognosis in endometrial cancer, also serve as a biomarker of better prognosis in colorectal cancer. In this large analysis, the presence of *POLE* mutations associated with a reduced risk of disease recurrence. *POLE* proofreading domain mutations define a subset of colorectal cancers that are more immunogenic resulting in greater immune activity and, therefore have a favourable prognosis. This novel biomarker shows promise to improve stratification of patients with colorectal cancer.

Addition of cetuximab to FOLFOX does not improve DFS in patients with type stage III colon cancer and specific RAS or BRAF types

Lead investigator Julian Taieb, Department of Gastroenterology and GI oncology, Université Paris Descartes, Hopital European George Pompidou in Paris, France and colleagues evaluated data from the PETACC8 trial of cetuximab plus FOLFOX versus FOLFOX in patients with full wild type RAS and BRAF stage III colon cancer to determine the prognostic value of mutated forms of these genes, which are known to confer resistance to anti-EGFR treatment. The investigators sequenced exons 2, 3 and 4 of KRAS and NRAS as well as BRAF exon 11 and 15 using the ampliseq colon lung cancer panel V2 in patients participating in PETACC8 who also signed informed consent for translational research. The relationship between cetuximab and time to recurrence (TTR), disease-free survival (DFS), and overall survival (OS) was assessed in patients with RAS wildtype, RAS and BRAF double wildtype tumours, and in patients with rare RAS mutations.

The analysis comprised 2559 patients; of these 745 (29%) patients were known to have tumours with KRAS exon 2 mutation and 163 (6.4%) had tumours harbouring BRAF V600E mutation. Of the remaining 1654 patients, 1054 had given informed consent for additional analyses and were assessed by next generation sequencing (NGS). NGS identified 227 (21%) patients that were newly diagnosed as KRAS exon 3,4 or NRAS exon 2,3,4 mutated, and 46 (4.4%) patients as having non-V600E BRAF mutated tumours.

The TTR, DFS, and OS were not improved with cetuximab in patients with RAS wild-type or RAS/BRAF double wild-type tumours (hazard ratio [HR] ranging from 0.77 to 1.05; all $p > 0.05$).

FOLFOX plus cetuximab did not have a significant deleterious effect in patients with RAS mutation patients (HR ranging from 1.13 to 1.29, all p > 0.05). No significantly different outcome was observed with and without cetuximab in patients with RAS or BRAF rare mutations (HR ranging from 1.42 to 1.61, all p > 0.05).

Pooled data from both treatment arms demonstrated that, in comparison to patients with double wild-type, patients with KRAS and NRAS codon 61 rare mutations were associated with poorer TTR; KRAS, HR 2.42; 95% confidence interval [CI] 1.40, 4.20 (p = 0.001), and NRAS, HR 2.18; 95% CI1.21, 3.93 (p = 0.008). DFS was similarly poorer in patients with these mutations; KRAS, HR 1.98; 95% CI 1.15, 3.42 (p = 0.01), and NRAS, HR1.99; 95% CI 1.13, 3.50 (p = 0.015). Other RAS or BRAF rare mutations did not associate with poorer TTR or DFS. EudraCT number 2005-003463-23. Taieb *et al.* Abstract 461O

Practice point and future research opportunities

Adding cetuximab to standard FOLFOX adjuvant therapy did not significantly improve outcome in patients with RAS wild-type and RAS/BRAF double wild-type of in patients with RAS mutant tumours. Rare mutations in NRAS or KRAS codon 61 were the only mutations detected in this trial that have the pejorative prognostic value similar to KRAS codon 12 and 13 or BRAF V600E mutations.

Phase III trial demonstrates 48 weeks of capecitabine adjuvant chemotherapy is not superior to conventional 24-week treatment in patients with stage III colon cancer: Final results of JFMC37-0801

Shigeki Yamaguchi, Gastroenterological Surgery, Saitama Medical University International Medical Center, Hidaka, Japan presented findings on behalf of colleagues from the JFMC37-0801 phase III study, which was designed to demonstrate the superiority of 48 weeks of capacitance adjuvant chemotherapy over the conventional duration of 24 weeks of capecitabine treatment. The primary endpoint was disease-free survival (DFS) in patients with stage III colon and rectosigmoid cancer. The trial enrolled patients with curatively resected stage III colon and rectosigmoid cancer, with performance status 0 to 1, aged 20 to 79 years that had not received prior therapy. The patients were randomly assigned to receive daily capecitabine at 1,250 mg/m^2 for 14 of 21 days for 24 weeks (n=654), or capecitabine at the same dose for 48 weeks (n=650). The primary endpoint was DFS, and the secondary endpoints were overall survival (OS) and relapse-free survival (RFS).

At data cut-off of March, 2016, median follow-up was 60 months and 434 DFS events were observed. The 3-year and 5-year DFS rates were 75.3% and 68.7% in the 24 week cohort versus 70.0% and 65.3% in the 48 week cohort, respectively, hazard ratio [HR] 0.866; 95% confidence interval [CI] 0.717, 1.046 (p = 0.068). Five-year OS rates were 87.6% in the 24 week and 83.2% in the 48 week arms, HR 0.737; 95%CI 0.557, 0.975 (p = 0.0259). The 5-year RFS was 74.1% versus 69.3% in the respective arms, HR 0.808; 95%CI 0.658, 0.992 (p = 0.0207). An increased incidence of hand-foot syndrome was observed in the 24-week cohort; however overall grade 3/4 adverse events were comparable in both arms. Yamaguchi *et al.* Abstract 469PD

Practice point and future research opportunities

Findings from this trial did not support the superiority of 48-weeks of treatment with capecitabine adjuvant chemotherapy over 24 weeks of capecitabine in patients with stage III colon cancer, in terms of DFS, the primary endpoint. However, regarding OS and PFS, the p-values for the comparison of 48 weeks treatment with 24 weeks treatment were less than 0.025, perhaps leaving the optimal duration of adjuvant chemotherapy for stage III colon cancer unresolved.

GASTROINTESTINAL TUMOURS - Non-colorectal

Olaparib in combination with paclitaxel did not improve survival over sole paclitaxel in patients with advanced gastric cancer that progressed on first-line therapy

Lead author Yung-Jue Bang, Department of Internal Medicine, Seoul National University Hospital (SNUH)-Yongon Campus, Seoul, Republic of Korea presented results of the phase III GOLD trial of olaparib added to paclitaxel in adult patients with advanced gastric cancer and at least one lesion that was detectable by imaging. The study included 525 patients from China, Japan, South Korea, and Taiwan with gastric and gastrooesophageal junction tumours who progressed following frontline therapy. Patients were randomised to olaparib at 100 mg tablet twice daily in combination with weekly paclitaxel at 80 mg/m^2 for a 28-day cycle or to receive the same dose of paclitaxel plus placebo. Tumour samples from resected tissue or a biopsy were tested for ATM expression, with 18% of the participants testing negative. The primary endpoint of the study was overall survival (OS) with secondary endpoints of progression-free survival (PFS), safety, and response.

Across the overall population, median OS was 8.8 versus 6.9 months, with and without olaparib, respectively (hazard ratio [HR] 0.79; 97.5% confidence interval [CI] 0.63, 1.0; p = .0262), which did not meet the primary endpoint. PFS was 3.7 months with olaparib/paclitaxel versus 3.2 months with paclitaxel alone (HR 0.84; 97.5% CI 0.67, 1.04; one-sided p = 0.157), The adjusted objective response rates were similar in each arm, odds ratio 1.69 (p = 0.0548). The trend towards OS benefit was independent of ATM status, the subgroup of patients that were ATM-positive demonstrated similar results to the overall population.

Adverse events (AEs) with the combination were similar to those seen with single-agent paclitaxel.

Grade ≥3 AEs occurred in 78% of patients treated with olaparib plus paclitaxel compared with 62% of those receiving paclitaxel alone. Serious AEs were higher in the paclitaxel/placebo arm compared with olaparib (35% versus 25%). The most common AE that led to a dose modification was neutropenia (54.1% with olaparib versus 37.1% with placebo). AEs leading to discontinuation occurred in 16% of combination and 10% of paclitaxel patients. D081BC00004; NCT01924533. Bang *et al.* Abstract LBA25

Practice point and future research opportunities

In the phase III Gold study, the combination of olaparib and paclitaxel failed to improve OS compared with paclitaxel and placebo for patients with advanced gastric cancer.

Olaparib is a selective inhibitor of PARP-1 and PARP-2 that is currently approved in the United States as a treatment for women with BRCA-mutant advanced ovarian cancer following three or more prior lines of chemotherapy. Additionally, the agent has received a breakthrough therapy designation as a potential treatment for men with BRCA1/2 or ATM-mutated metastatic castration-resistant prostate cancers. Outside of gastric cancer, a number of phase III studies

continue to assess olaparib for patients with cancer across a variety of indications, including breast, pancreatic, and prostate cancer. A study is exploring the agent as an adjuvant treatment for patients with BRCA-mutant, HER2-negative breast cancer (NCT02032823), and another is assessing frontline olaparib for patients with germline BRCA-mutant pancreatic cancer (NCT02184195). Phase III studies are also assessing the combination of olaparib with the angiogenesis inhibitor cediranib (NCT02502266, NCT02446600).

Irinotecan added to S-1 significantly improves PFS over S-1 alone in patients with advanced esophageal squamous cell carcinoma that failed platinum- or taxane-based chemotherapy

Juan Huang, of the Medical Oncology Department, Cancer Institute and Hospital, Chinese Academy of Medical Sciences, in Beijing, China, and colleagues conducted a phase III trial in patients with advanced oesophageal squamous cell carcinoma that was refractory to platinum-based or taxane-based first-line chemotherapy. The patients were randomised to irinotecan at 160 mg/m^2 intravenously on day 1 every 2 weeks plus S-1 at an initial oral dose of 40 to 60 mg twice a day on days 1-10 every 2 weeks or to S-1 at an initial oral dose of 40 to 60 mg twice a day on days 1-14 every 3 weeks. The patient baseline characteristics were similar between the 53 patients receiving irinotecan/S-1 and the 49 patients receiving S-1 only; approximately 85% were aged 65 or younger, 90% were male, and 90.6 versus 81.6% of patients in the irinotecan/S-1 arm versus S-1 arm had 0 to 2 metastatic sites. The primary end point was progression-free survival (PFS), and secondary end points included response rate, disease control rate (DCR) and overall survival (OS).

At an interim analysis, superior efficacy with the combination treatment over S-1 alone was observed; significantly improved median PFS of 3.9 months with irinotecan and S-1 versus 1.8 months with S1 only (p = 0. 0019) was demonstrated. The response rate was doubled at 28.3% with irinotecan and S-1 compared to 12.2% in the S1 arm (p = 0.045). Median OS was numerically longer with irinotecan and S-1 at 7.0 months compared to 6.3 months with S-1 (p = 0.2622). The most frequently reported adverse events in the irinotecan and S-1 arm were nausea, vomiting, and neutropenia. NCT02319187. Huang *et al.* Abstract LBA27

Practice point and future research opportunities

No standard second-line treatment has been determined for patients with advanced oesophageal squamous cell carcinoma following failure of prior platinum- or taxane-based chemotherapy. These phase III trial results indicate that PFS is improved with the addition of irinotecan to S-1 therapy over sole S-1 in this setting.

Regorafenib represents a potential second-line treatment option for patients with HCC that progress on sorafenib

Jordi Bruix, Liver Unit Hospital Clinic, University of Barcelona in Barcelona, Spain presented results from the phase III RESOURCE trial of regorafenib in patients with hepatocellular carcinoma (HCC) who progress on sorafenib. The investigators enrolled 573 patients from centres in 21 countries who were stratified by Asia versus non-Asia, the presence/absence of microvascular invasion or extrahepatic disease, ECOG performance status of 0 versus 1, and α-fetoprotein less than 400 ng/mL versus 400 ng/mL or greater. All patients had Barcelona Clinic Liver Cancer (BCLC) stage B or C designated HCC plus documented radiologic progression after a minimum of 20 days of sorafenib at 400 mg or more per day. Baseline characteristics were balanced between the regorafenib and placebo arms. The patients' median age was 63 years, 88% were male, and 87% of patients had BCLC stage C disease. The patients were randomised 2:1 to oral regorafenib at 160 mg or placebo once daily for 1 to 3 weeks of a 4-week cycle. The median treatment duration was 3.6 (range: 0.03 to 29) months for regorafenib versus 1.9 (range: 0.2 to 27) months for placebo.

Regorafenib improved overall survival (OS), the trial's primary endpoint, by nearly 3 months over placebo; median OS was 10.6 months versus 7.8 months, respectively. Regorafenib patients had a 38% reduction in the risk of death and a 54% reduction in the risk of progression compared to placebo. Patients receiving regorafenib also demonstrated significantly prolonged median PFS of 3.1 compared to 1.5 months in patients receiving placebo, hazard ratio [HR] 0.46 (p <0 .001). Similarly, median time to progression (TTP) was 3.2 versus 1.5 months with regorafenib versus placebo, respectively, HR 0.44 (p <0 .001). A higher disease control rate of 65.2% was observed with regorafenib compared to 36.1% with placebo (p < 0 .001), and 10.6% of patients receiving regorafenib showed either complete or partial response versus 4.1% of placebo patients (p = 0.01).

Treatment emergent adverse events (TEAEs) grades 3/4 occurred in 58% versus 29% and drug related TEAEs leading to treatment interruption occurred in 42% versus 8% of patients in the regorafenib and placebo arms, respectively. The most commonly reported grade adverse events ≥3 were hypertension (15.2% versus 4.7%), hand–foot skin reactions (12.8% versus 0.5%), fatigue (9.1% versus 4.7%), and diarrhoea (3.2% versus 0.0%) in the respective arms.

Quality of life data that was collected using the EQ-50 index, EQ-50 VAS, Fact-G, FACT-Hep total, and Trial Outcome scales demonstrated significant differences between patients receiving regorafenib and placebo only on the last 2 scales; the difference between the groups was -8.85 on the FACT-Hep total, and -4.05 on the Trial Outcome Index (both p < 0.001). NCT01774344. Brix *et al.* Abstract LBA28

Practice point and future research opportunities

No second-line systemic treatment options have been approved to date for hepatocellular carcinoma. Regorafenib, an oral multikinase inhibitor, treatment resulted in a higher response rate and disease control rate that was twice that of placebo in patients with late stage

hepatocellular carcinoma who progressed during sorafenib treatment. Results from this phase III trial also showed that regorafenib significantly improved overall survival in these patients. Regorafenib may have the potential to become the standard of care as second-line treatment in patients with previously treated hepatocellular carcinoma that are unsuited to loco-regional therapy and have progressed on sorafenib because regorafenib significantly improved overall survival over placebo.

Arguments against regorafenib as second-line treatment in this setting state that no clinically meaningful differences in patient-reported quality of life outcomes were observed on most scales between patients treated with regorafenib and placebo, and there was a high rate of regorafenib treatment interruption due to adverse events, suggesting that regorafenib was not well-tolerated. However, nearly 50% of patients with hepatocellular carcinoma in this study received the full dose of regorafenib.

Centralisation of surgery is the key to lowing the risk of post-operative mortality in oesophago-gastric cancer patients

Caroline Gronnier, Department of Digestive and Oncological Surgery, Lille University Hospital in Lille, France and colleagues conducted a systematic review of all 11,196 consecutive patients undergoing oesophago-gastric cancer surgery in France between 2010 and 2012 to determine whether centre volume impacted postoperative mortality (POM). The investigators compared the 30- and 90-day POM according to the centre volume in patients attending the centre. Each centre was categorised by low or less than 20 cases per year, intermediate with 20 to 39, or high with 40 to 59, and very high, which was defined a 60 or more cases per year. Centres were also evaluated following stratification of patients by Charleson scores of 0, 1-2, ≥3. The patients were sub-grouped into the oesophageal cancer group with 3286 patients and 7910 patients comprised the gastric cancer subgroup for comparisons of 30-day and 90-day POM per centre.

The majority, 64.2% of patients overall, were treated in low-volume centres. However, a reduction in the relative risk of nearly 70% in both 30- and 90-day POM was observed in very-high versus low volume centres, that remained constant regardless of the patient's Charleson score or tumour location. An inverse relationship between decreasing POM rates was observed as the volume of the centre increased; a significant linear decrease in 30- and 90-day POM was observed with increased centre volume. The rates for 30-day POM were 5.7%, 4.3%, 3.3%, and 1.7%, whereas the rates for 90-day POM were 10.2%, 7.9%, 6.7%, and 3.6% in low-, intermediate-, high- and very high-volume centres, respectively ($p < 0.001$). The comparison of low- and very high-volume centres by Charleson score showed 30-day POM rates were 4.0% versus 1.1% for the patients with a Charleson score of 0 ($P=0.001$), 7.5% versus 3.4% for Charleson scores 1-2 ($p < 0.001$), and 14.7% versus 3.7% for Charleson scores ≥3 ($p = 0.003$). Assessment of the oesophageal and gastric cancer subgroups demonstrated a similar linear decrease. Gronnier *et al.* Abstract 609O

Practice point and future research opportunities

Recent reports have demonstrated that centralisation of cancer services improves the outcome and quality of care for patient, and centralisation has been particularly recommended for less common cancers. This large analysis of a French database demonstrated that the risk of 30- and 90-day post-operative mortality was significantly reduced as the case-volume of the centre increased, with the risk substantially lower in very high volume centres, indicating that oesophago-gastric cancer surgery should be centralised to reduce the risk of post-operative mortality. The patients fared better in high volume centres irrespective of the patient's Charleson score or the location of the tumour.

Next generation sequencing of oesophagogastric adenocarcinomas identifies molecular signatures that correspond to response following HER2 inhibition, first-line 5FU/platinum and PD1/CTLA4 blockade

Yelena Y. Janjigian, of the Memorial Sloan-Kettering Cancer Center, in New York, USA reported that her team was able to identify several potential therapeutic targets that were specific to oesophagogastric (EG) subtypes of adenocarcinoma by next generation sequencing (NGS). The putative targets included receptor tyrosine kinase (RTK) alterations in tumours with chromosomal instability, in tumours driven by the Epstein-Barr Virus (EBV), and tumours with microsatellite instability (MSI). DNA from patients with stage IV EG adenocarcinoma was evaluated using the NGS MSK-IMPACT assay, which is capable of detecting somatic mutations, deletions and amplifications and determined the association of these results with clinical outcomes.

The investigators analysed 429 tumours from 319 patients with stage IV EG adenocarcinoma; of these, 33% were from the oesophagus, 52% were of gastric origin, and 15% were located at the gastro-oesophageal junction (GEJ). Of the 80 HER2-positive tumours, as determined by immunohistochemistry and FISH, 71 were obtained prior to treatment with trastuzumab and 38 were taken afterwards; there were also 28 paired pre/post samples.

An evaluation of the paired samples showed a post-therapeutic loss of HER2 amplification in 16% of cases, the gain of new MET amplification in 7%, new amplification of EGFR in 4%, and new amplification of IGF1R in 4% of cases. Investigation of the paired samples also showed new mutations post-treatment in 14% of ERBB4 case, 11% of KRAS, 7% of PIK3CA, and 7% of cases showed newly mutated mTOR.

Analysis of the post-treatment tumours revealed co-occurring EGFR/HER2 amplification in 4 of 20 patients receiving afatinib, which corresponded to 3 of these patients achieving partial response (PR). In 20 (6%) of patients with deleterious somatic (n=15) or germline (n=5) BRCA1/2 mutations, 4 of 5 patients with BRCA1/2 germline showed loss of the wild-type allele and exhibited dramatic tumour regression following 5FU/platinum treatment; of these, 2 patients achieved complete response (CR) with a time to progression ranging from 15 to 22 months, and demonstrated overall survival (OS) of 18 to 35 months. The one patient with germline BRCA1 but without loss of heterozygosity experienced rapid disease progression and OS of just 9 months. One patient with an inactivating somatic BRCA1 mutation (germline wild-type) and LOH

achieved CR after receiving 5FU/platinum that is ongoing at 28 months. MSI tumours were reported in 12 (4%) of patients; 3 of these patients were treated with an anti-PD1 agent, which resulted in one patient achieving a CR that was durable at 14 months, and one patient each demonstrated PR and stable disease after 3 months of therapy. One patient with a microsatellite stable EBV-positive tumour that was treated with PD1/CTLA4 blockade achieved a CR that is ongoing at 17 months. Patients acquiring trastuzumab resistance demonstrated loss of ERBB2 amplification and secondary alterations in the RTK/RAS/PI3K pathway. NCT01775072. Janjigian *et al.* Abstract 612O

Practice point and future research opportunities

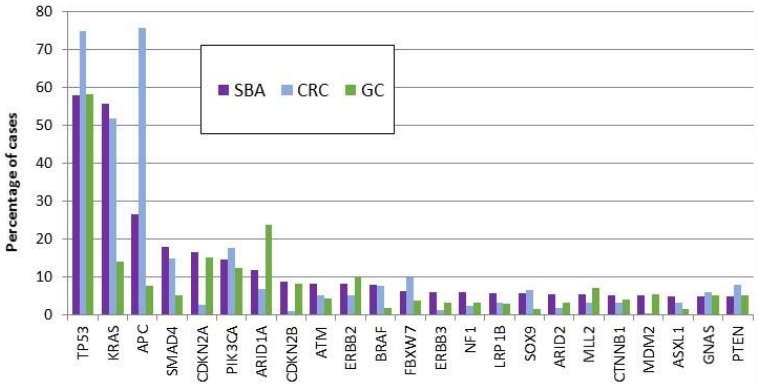
The study supports testing of patients with oesophagogastric cancer for germline and somatic BRCA1 and BRCA2 by next generation sequencing which may identify patients most likely to respond to platinum-based chemotherapy. Promising activity was observed with immunotherapy in patients having microsatellite instability and EBV+ tumours.

Comprehensive genomic profiling identifies potentially actionable mutations in small bowel adenocarcinoma

Results from the largest and most comprehensive genomic characterisation of 3 large series of small bowel adenocarcinoma (SBA) revealed different mutational frequencies in SBA, colorectal carcinoma (CRC), and gastric carcinoma (GC) that were potentially druggable, according to Alexa Schrock, Clinical Development, Foundation Medicine in Cambridge, USA. Dr. Schrock and colleagues used hybrid-capture based comprehensive genomic profiling (CGP) to prospectively analyse clinical samples from 358 patients with SBA, 6,353 patients with CRC, and 889 patients with GC. Complete molecular profiles were prepared and compared with available clinical features. The majority (52-55%) of patients in the 3 series were male; SBA patients tended to be marginally older than the patients with the other two cancer types with a median age of 60 years.

The alterations identified included APC alterations, which occurred at a frequency of 76% in CRC and 27% in SBA ($p < 0.001$). BRAF alterations were found in 8% each of CRC and SBC samples. BRAF V600E mutations occurred less commonly in SBA, and represented just 10% of BRAF-mutated samples in this series. ERBB2 and EGFR amplifications were detected more often in GC, but ERBB2 (7%) and EGFR (1.4%) point mutations were most common in SBA compared to the other tumour types tested.

High microsatellite instability (MSI-H) more frequently occurred in SBA (6.9% of cases) than in CRC (3.9%), or GC (4%). Targetable alterations including EGFR and ERBB2 alterations, BRAF mutations, PI3K pathway and MEK1 mutations, and RTK fusions were detected in all three series, according to Dr. Schrock, who noted that one SBA patient whose tumour harboured a GOPC-ROS1 fusion had demonstrated a clinical response to the ALK/ROS1 inhibitor crizotinib.



Gene	P-Value		
	SBA vs CRC	SBA vs GC	CRC vs GC
TP53	<0.0001	0.9784	<0.0001
KRAS	0.1678	<0.0001	<0.0001
APC	<0.0001	<0.0001	<0.0001
SMAD4	0.1587	<0.0001	<0.0001
CDKN2A	<0.0001	0.6281	<0.0001
PIK3CA	0.1379	0.3823	0.0001
ARID1A	0.0004	<0.0001	<0.0001
CDKN2B	<0.0001	0.7599	<0.0001
ATM	0.0137	0.0080	0.3357
ERBB2	0.0099	0.4351	<0.0001
BRAF	0.8167	<0.0001	<0.0001
FBXW7	0.0320	0.0821	<0.0001
ERBB3	<0.0001	0.0226	0.0002
NF1	<0.0001	0.0302	0.1241
LRP1B	0.0103	0.0288	0.8614

Frequency of genomic alterations in SBA, CRC and GC.
Graph includes genes altered in > 5% of SBA cases in this series. Corresponding P values comparing frequency of alteration a gene across tumor types. Cases for which the difference was statistically significant (P <0.05) are highlighted in green.

Frequency of genomic alterations in small bowel adenocarcinoma, colorectal carcinoma, and gastric carcinoma.

© Alexa Schrock.

Overall, the molecular profile of SBA was distinct from either CRC or GC, and the genomic alterations identified in unspecified SBA were similar to those identified in duodenal adenocarcinoma. The authors also noted that the higher incidence of microsatellite instability identified in SBA suggests that a subset of patients with SBA may benefit from treatment with anti-PD-1/PD-L1 therapies. Schrock *et al.* Abstract 613O

Practice point and future research opportunities

Small bowel adenocarcinomas are cancers that occur rarely and have a lower incidence than other intestinal derived cancers. Since diagnosis is often made at a later stage, patients often have poorer overall survival than patients with colorectal or gastric cancer. This study offers the first large scale genomic comparison of the 3 cancer types, as well as a comparison of unspecified small bowel adenocarcinomas with tumours of the duodenum. It illustrates that using comprehensive genomic profiling over the course of clinical care can identify targetable genomic alterations across diverse intestinal tumour types and allows patients to be matched with appropriate targeted therapies.

Nivolumab demonstrates efficacy in patients with advanced HCC

Ignacio Melero, Laboratory of Immunology, Universidad de Navarra, Pamplona, Spain, presented interim data on behalf of colleagues from the phaseI/II CheckMate-040 study of nivolumab in patients with histologically confirmed advanced hepatocellular carcinoma (aHCC). CheckMate-040 comprises 2 cohorts: 48 patients had completed the dose escalation portion of the trial and had previously failed, refused, or who were intolerant to sorafenib and were subcategorised into uninfected, infected with the hepatitis B virus (HBV), or infected with hepatitis C (HCV), patients in this cohort received nivolumab at 0.1 to 10 mg/kg for up to 2 years and had Child-Pugh scores ≤7; the expansion cohort comprised 214 patients subcategorised as uninfected and sorafenib naive/intolerant, uninfected patients progressing on sorafenib, HBV-infected, and HCV-infected patients, in this cohort, Child-Pugh scores were ≤6 and patients were treated with nivolumab at 3 mg/kg across all subgroups. The primary endpoints were safety in the escalation cohort, overall response rate (ORR) by RECIST 1.1 in the expansion cohort, and other endpoints included overall survival (OS), duration of response (DOR), and assessment of PD-L1 expression status. At baseline, 85% of escalation versus 75% of expansion patients had a Child Pugh score 5, extrahepatic lesions were present in 77% versus 75%, and 77% versus 68% had received sorafenib in the escalation versus expansion arms, respectively.

The interim analysis revealed nivolumab was effective regardless of the underlying aetiology of HCC or the degree of PD-L1 expression. The ORR in the escalation and expansion cohorts were 15% and 15%, with 3 (6%) versus 2 (1%) patients in the respective cohorts achieving complete responses (CR), while 4 (8%) versus 33 (15%) had partial responses (PR). Stable disease was experienced by 24 (50%) versus 11 (52%) and disease progression occurred in 15 (31%) versus 63 (29%) of escalation and expansion patients, respectively. The median DoR was months 17 months, the median OS was14.3 months, and the OS rate was 59.1% at 12 months in the escalation cohort. Median DoR, OS and the OS rate at 12 months were not reached in the expansion cohort. Response across all subcategories was similar to the response observed in the overall cohort, regardless of infection or prior sorafenib.

Treatment with nivolumab was generally safe and well-tolerated; 65% of expansion patients experienced any drug-related adverse events (AEs), including 18% with grade 3/4 events. The most commonly reported treatment-emergent AEs grade 3/4 were ALT, AST, and amylase elevations, which occurred in 3%, 4%. And 3% of expansion patients, respectively. Tolerability profiles in the escalation cohort were consistent with the expansion cohort and were previously reported. Melero *et al.* Abstract 615O

Practice point and future research opportunities

The RR with nivolumab in this study of patients with HCC compare favourably with the ORR of approximately 2% with sorafenib, the current first-line indication. An encouraging 12-month overall survival was also observed; both the objective response and OS rates for the escalation cohort compare favourably with historic best supportive care data. In addition, nivolumab

monotherapy had a manageable safety profile in patients with hepatocellular carcinoma, including those with HBV or HCV infection, and showed durable responses across all dose levels and aetiologic cohorts, and in patients with high PD-L1 expression, which has been associated with a poorer prognosis in hepatocellular carcinoma. Further evaluation of nivolumab is ongoing in this trial and warranted.

No statically significant added benefit with intraperitoneal paclitaxel plus S-1/paclitaxel over standard chemotherapy in patients with gastric cancer and peritoneal metastasis

Primary author Yoshiyuki Fujiwara, Department of Gastroenterological Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan presented findings from the phase III PHOENIX-GC trial of intraperitoneal paclitaxel plus S-1/paclitaxel compared with S-1/cisplatin in patients with gastric cancer patients and peritoneal metastasis. The trial enrolled 183 patients with pathologically confirmed gastric adenocarcinoma and peritoneal metastasis that had either received no chemotherapy or short-term chemotherapy lasting less than 2 months. Patients were randomised 2:1 to the IP arm where they received intraperitoneal paclitaxel at 20 mg/m^2 plus intravenous paclitaxel at 50 mg/m^2 on days 1 and 8 plus S-1 at 80 mg/m^2/day on days 1 to 14 every 3 weeks or to a SP arm of intravenous cisplatin at 60 mg/m^2 on day 8 plus S-1 80 mg/m^2/day on days 1 to 21 every 5 weeks. Randomisation was stratified by centre, prior chemotherapy, and the extent of peritoneal disease. The primary endpoint was overall survival (OS) and secondary endpoints included response rate and safety.

The efficacy analysis included 164 patients and showed well-balanced baseline characteristics in both arms, except for ascites; 38 (84%) patients with ascites beyond the pelvic cavity were randomised to the IP arm versus 7 (16%) to the SP arm.

Although a trend towards improved OS was seen in the IP arm, the primary analysis did not support statistical superiority of the IP over the SP regimen; the median OS for the IP and SP arms was 17.7 and 15.2 months, respectively (stratified log-rank test, p = 0.080; hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.49, 1.04; p = 0.081). However, adjustment for the baseline ascites by sensitivity analysis using a stratified Cox regression model yielded HR 0.59 (95%CI 0.39, 0.87, p=0.0079) for the comparison of the two regimens. The response rates were 53% in the IP arm versus 60% in the SP arm (p = 1.0). Subgroup analysis revealed that female patients, patients with histologically undifferentiated tumours, and patients with ascites beyond the pelvic cavity had prolonged OS with IP regimen. The safety profile was similar in both arms and demonstrated that both regimens were tolerable. UMIN000005930. Fujiwara *et al.* Abstract 616PD

Practice point and future research opportunities

Efficacy with intraperitoneal paclitaxel has been reported in ovarian cancer due to the sustained high local concentrations provided. The authors showed prior promising results with intraperitoneal paclitaxel plus with S-1/paclitaxel in gastric cancer. This phase III study did not show statistically significant superior efficacy with intraperitoneal paclitaxel plus with S-

1/paclitaxel compared to standard systemic chemotherapy in gastric cancer with peritoneal metastasis, although a sensitivity analysis, adjusting for an imbalance of patient's ascites in the treatment arms, suggested clinical efficacy of intraperitoneal paclitaxel plus with S-1/paclitaxel. Subgroup analysis suggested that female patients, those with undifferentiated tumours and patients with ascites beyond the peritoneal cavity may derive greater benefit from the intraperitoneal regimen.

Molecular characteristics vary among patients with HCC according to age group

Celina Ang, Department of Haematology Oncology of the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai in New York, USA and colleagues evaluated gene sequencing, amplification, and protein expression data from 421 hepatocellular carcinoma (HCC) specimens to determine whether molecular characteristics differ among patients with HCC according to age. They noted that in the Western hemisphere patients are usually diagnosed with HCC in the middle years and HCC is less frequently diagnosed in young adults or the elderly, whereas world-wide HCC diagnoses at the extremes of the age spectrum are associated with distinct geography and aetiologies. The investigators stratified patients with HCC into subgroups of young adult, aged 18-39 years, intermediate aged 40 to 74 years, and elderly, aged 75 years and more for comparison of molecular characteristics associated with HCC. Only pathogenic or presumed pathogenic (P/PP) mutations were analysed and the Chi-square test was used for statistical comparisons.

The data revealed 39 young adults, 336 intermediate aged, and 46 elderly patients were diagnosed with HCC. In the young adult subgroup, 54% of patients were female compared to 23% of intermediate aged ($p < 0.0001$), and 33% of elderly patients ($p = 0.0483$). Young adults had lower MRP1 expression of 60% versus 86% in intermediate ($p=0.04$), and 95% in elderly patients with HCC ($p = 0.02$). PDGFR and PD-L1 expression was not observed in this subgroup and PIK3CA, PTEN, and PTPN11 mutations were also not detected in young adults. One ATM mutation was detected in young adult patients but in no other age group. The overall frequency of P/PP mutations was 0.38 in young adults compared with 0.71% of intermediate aged ($p = 0.012$), and 0.93 in elderly patients ($p = 0.038$). MGMT was expressed in 71% of intermediate aged patients versus 49% in young adults ($p = 0.007$), and SPARC was expressed in 13% of elderly patients but not in young adults ($p = 0.005$). PDGFR and PD-L1 were expressed in 14% and 19% of intermediate aged versus 29% and 17%, respectively, of elderly patients. Of 47 genes analysed, TP53 was the most frequently altered in young adults at 19% of cases, while CTNNB1 was the most frequent in 30% of intermediate aged, and 33% of elderly patients compared with just 9.5% of young adults.

Among male patients, androgen receptor (AR) expression was much lower in young adults at 6% versus 35% in intermediate aged ($p = 0.02$), and 32% in elderly patients ($p = 0.05$), whilst among females, expression of the AR increased with age from 6%, to 7% and to 15% in young adult, intermediate, and elderly patients, respectively ($p > 0.05$). PIK3CA, PTEN, and PTPN11 mutations were more prevalent in the elderly and occurred in 13.3%, 7.1% and 6.7%, of elderly

patients, respectively, versus 1.4%, 0.7% and 0% of intermediate aged patients (all $p < 0.05$). ANG *et al.* Abstract 618PD

Practice point and future research opportunities

This study showed an association between female sex, decreased drug resistance protein, and AR expression with young adult patients diagnosed with HCC, indicating that these patients may be more sensitive to alkylating agents. The data also suggest that elderly patients with HCC may derive more benefit from PIK3CA/Akt/mTOR or MAPK pathway inhibitors. These findings warrant further investigation and may provide information that is useful to the network of cancer centres planning prospective studies; which may be improved by the incorporation of aetiological factors and molecular features.

The lymph node ratio is a prognostic factor in curative treatment of gallbladder cancer

Immediate radical re-resection (IRR) is often needed after simple cholecystectomy for incidental gallbladder carcinoma (IGBC) and the forthcoming S3- guidelines will extend the current recommendations for aggressive surgery in T2 and more advanced stages to patients with stage T1b, according to Thorsten O. Goetze, Institute of Clinical Cancer Research, Nordwest-Krankenhaus, Frankfurt Am Main, Germany. This change is based upon data from the German-Registry, the largest gallbladder cancer registry in Europe, which showed the indication for IRR depended more on the experience in liver surgery of the hospitals than on guideline compliance. This suggested to the authors that most of patients with IGBC could be staged incorrectly and do not receive sufficient therapy. The investigators used data from the German Registry for this analysis of 950 cases of IGBC.

From this analysis, it has emerged that an IRR was performed in 42 of 113 T1b cases which yielded a significant survival benefit for these T1b patients. A survival benefit was also seen for the 228 patients with stage T2 and 80 patients with stage T3 that were treated with IRR compared to the 461 patients with T2 and 215 patients with T3 tumours not receiving IRR. The investigators found that good results were obtained with the wedge resection technique in T1b and T2 patients but stage T3 disease showed better results with more radical techniques.

To date, less than 50% of T2–3 tumours in the registry have been re-resected. According to the authors, local resection was performed significantly more often in high-volume clinics. The lymph node ratio could be calculated in 212 patients, which emerged as a significant prognostic factor in gallbladder cancer. The investigators are planning a multimodal therapy trial that has the support of over 300 clinics to further improve the cure rate in T2-3 gallbladder cancer patients. Goetz *et al.* Abstract 619PD

Practice point and future research opportunities

This analysis provides data supporting radical surgery for patients with incidental gallbladder cancer up to stage T1b and that the wedge resection technique provides good results in stages

T1b/T2 due to the lower invasiveness. Implementation of these recommendations should also be possible in low volume institutions having little experience in liver surgery. The study also describes the utility of the lymph node ratio as a prognostic factor in gallbladder cancer.

Comparative molecular analyses of pancreatic cancer in younger and older patients

Mohamed E. Salem, Division of Haematology and Oncology, Lombardi Cancer Centre, Georgetown University, Washington, DC, USA, remarked that less is known about the molecular tumour characteristics and outcome in younger patients with pancreatic cancer, leading Dr. Salem and colleagues to examine 2426 pancreatic tumours to evaluate the molecular profiles of these tumours and to determine the association to outcome in younger versus older patients. The investigators reviewed protein expression by immunohistochemistry, gene amplification and sequencing data of the tumours to correlate genetic alterations with outcome. The comparison between age groups was made by Chi-squared test and survival estimates were by Kaplan-Meier methodology.

This large analysis revealed the most frequently mutated genes in this cohort of pancreatic tumours: KRAS was altered in 85% of tumours, TP53 in 63%, SMAD4 in 13%, BRCA2 in 12%, ATM/APC/NTRK1 in 5% each, BRCA1 in 4%, and cMET/PIK3CA were each altered in 3% of cases overall. The molecular profile of 568 tumours from the subgroup of younger patients with median age of 50 (range: 21 to 55) years was then compared to the profiles of 1113 tumours from older patients with a median age of 71 (range: 65 to 90) years. Interestingly, comparison between the age groups yielded a different profile for each. The tumours from younger versus older patients showed a greater frequency of mutations in MLH1 at 4% versus 0.3% ($p = 0.003$), PTEN at 3% versus 0.5% ($p = 0.008$), CTNNB1 at 2.3% versus 0.5% ($p = 0.04$), and c-KIT at 2% versus 0.3% ($p = 0.02$), respectively. Two genes were altered in younger patients' tumours but not in older patients: EGFR at 2.2% ($p = 0.003$), and NTRK1 at 20% ($p = 0.002$); however, NTRK1 was assessed in only 10 younger and 45 older patients' samples. Younger patients had higher TOP2A expression of 59% versus 50% in older patients ($p = 0.02$).

Older patients showed significantly higher KRAS mutations of 80% versus 70% in younger patients ($p = 0.0003$), as well as higher rates of low RRM1 expression at 85% versus 79% ($p = 0.03$) and high PDGFR expression of 22% versus 7% ($p = 0.03$), respectively.

Similar mutation rates were seen in some specific genes when older versus younger patient samples were compared: BRCA1 was 5%, BRAF was1%, and PIK3CA was 3% in both subgroups. BRCA2 was altered in 14% versus 12%, GNAS at 2.4% versus 1.6%, NOTCH1 at 0.9% versus 1.6%, cMET at 2.8% versus 3.9%, and RET was altered in 0.4% versus 0.8% in the respective older versus younger patient subgroups. PD-L1 expression in tumour cells was also similar in both age groups at 8% versus 7%, and on tumour-infiltrating lymphocytes at 41% versus 37% in older versus younger patients, respectively.

Outcomes were evaluable for 73 patients. Although no survival differences were observed between the age groups, lower expression of ERCC1, MGMT, PRM1, and TLE3 appeared to be associated with prolonged survival in older but not younger patients. The authors commented that larger studies are needed to confirm and define the significance of this finding. Salem *et al.* Abstract 620PD

Practice point and future research opportunities

This large analysis made a start in defining the genetic landscape of pancreatic cancer and determined that some genetic alterations harboured in pancreatic tumours of younger patients may differ from older patients, whereas the frequency of mutation for several genes was similar. A wider gene panel would aid in the discovery of targetable mutations.

GENITOURINARY TUMOURS - PROSTATE

Custirsen provides no additional survival benefit to cabazitaxel/prednisone in metastatic prostate cancer

Karim Fizazi, head of the Department of Cancer Medicine at the Institut Gustave Roussy, Villejuif, France expressed disappointment with the results from the AFFINITY trial of custirsen in metastatic, castration-resistant prostate cancer but noted that custirsen remains a viable candidate currently under evaluation in non-small cell lung cancer, as failure in one tumour type does not predict the outcome in other indications. Custirsen blocks production of the protein clusterin, which is upregulated in tumour cells following treatment interventions such as chemotherapy, hormone ablation, and radiation therapy and is overexpressed in a number of cancers, including prostate, lung, breast and bladder. Clusterin promotes carcinogenesis and tumour growth, and may contribute to treatment resistance.

Professor Fizazi and colleagues conducted the phase III AFFINITY trial in 635 patients with metastatic, castration-resistant prostate cancer, who had previously been treated with docetaxel. The patients were randomised 1:1 to 21-day cycles of custirsen at 25 mg/m2 i.v. plus cabazitaxel/prednisone or cabazitaxel/prednisone plus placebo, until disease progression, unacceptable toxicity, or ten cycles.

Median overall survival (OS) at 14.2 months in the custirsen arm compared to 13.4 months in the placebo arm (p = 0.529). Findings from an analysis of 62% of patients who met the criteria for poor prognosis supported this result, and demonstrated median OS of 11.1 with custirsen and 10.9 months with placebo.

Similar numbers of patients, 28.9% in the custirsen arm and 25% in the placebo arm, discontinued the study due to progressive disease. Discontinuation due to adverse events was also similar; 21.9% of patients receiving custirsen and 18.9% of patients on placebo halted treatment. The incidence of adverse events grade 3 and higher was similar between arms with the most frequently reported being neutropenia, anaemia, fatigue, asthenia, bone pain, and febrile neutropenia. NCT01578655. Fizazi *et al.* Abstract LBA9_PR

Practice point and future research opportunities

Treatment failure is the major barrier to extending survival in patients with advanced cancer. Custirsen was designed to block clusterin, a cytoprotective protein that is upregulated by chemotherapy and other treatment in cancer cells. Although the outcome of this trial was negative, the evaluation of custirsen in prostate cancer was conducted on the basis of solid preclinical and clinical evidence supporting anti-tumour activity. A previous phase II trial of custirsen combined with chemotherapy in men with metastatic castration-resistant prostate cancer suggested inhibition of clusterin may lead to improved clinical outcome, and an earlier phase III trial of custirsen in combination with docetaxel suggested patients with more aggressive

cancers may benefit from the combination. An ongoing trial of custirsen may contribute to evidence.

Phase II findings show alisertib has benefit in patients with neuroendocrine prostate cancer

Himisha Beltran, Division of Hematology and Medical Oncology at Weill Cornell Medicine in New York, USA presented phase II findings demonstrating that aurora kinase A inhibition with alisertib may benefit a subset of patients with neuroendocrine prostate cancer (NEPC). NEPC is an aggressive subtype of castration resistant prostate cancer that is androgen independent, and preclinical studies demonstrated that NEPC signalling supporting tumour growth could be suppressed with alisertib, which targets Aurora A and blocks the interaction between Aurora A and N-myc.

Dr. Beltran and colleagues enrolled 59 patients with metastatic prostate cancer in this multicentre, phase II trial to receive alisertib at 50 mg twice daily for 7 days of a 21-day cycle. Of these, 41 (70%) patients had at least one additional pathologic criteria, including NEPC morphology, greater than 50% neuroendocrine marker by immunohistochemistry, new liver metastases but without prostate specific antigen (PSA) progression, and/or greater than 3 to 5 times elevated serum NSE/CgA concentration. The patients' median age was 67 (range: 45 to 87) years, median PSA was 1.13 ng/ml (range: 0.01 to 514.2), and the patients had received prior therapy with docetaxel, platinum and abiraterone/enzalutamide. The metastatic sites were bone in 78%, lymph node in 73%, liver in 61% and lung in 37% of patients.

Among the evaluable 56 patients, median overall survival (OS) was 38 weeks and the 6-month progression-free survival (PFS) rate was 11.1% overall, but rose to 16.3% in the cohort of patients with pathologically defined NEPC. Among the 17 patients with scans taken at cycle 3, median PFS was 20 weeks and 6-month PFS was 35.8%. An exception response was seen in 2 patients, one of which demonstrated complete resolution of liver metastasis, and a third patient achieved stable disease lasting 39 months at follow-up. No new toxicity signals were raised and grade 3/4 toxicities occurred in 5 (9%) patients. NCT01799278. Beltran *et al.* Abstract LBA29

Practice point and future research opportunities

Alisertib is being explored across a broad range of haematological malignancies and solid tumours, including phase III trials in refractory T- and B-cell lymphoma. These findings suggest that alisertib may be beneficial in some patients with neuroendocrine prostate cancer. The authors are continuing genetic analyses and the results may allow the integration of clinical, pathologic, and molecular features that may help to improve patient selection and enhance outcome following alisertib.

Meta-analysis supports metastasis-free survival as a surrogate for OS in localised prostate cancer

Wanling Xie, Department of Biostatistics and Computational Biology, Dana-Farber Cancer

Institute, Boston, USA presented finding from a meta-analysis on behalf of colleagues in the Intermediate Clinical Endpoints in CaP (ICECaP) Working Group that attempted to identify surrogate end points that correlate with overall survival in localised prostate cancer clinical trials. The investigators analysed data from 12,712 men included in 19 mature randomised clinical trials conducted between 1987 and 2010. Of those, 90% of patients were from radiotherapy-based studies, 30% had intermediate-risk disease, and 57% had high-risk disease.

Metastasis-free survival (MFS) was defined as the time from randomisation to the first evidence of distant metastatic disease, excluding pelvic lymph nodes, or death from any cause, and overall survival (OS) as the time from randomisation to death from any cause. At a median follow-up of 9.9 years, there were 5733 MFS events and 5350 OS events. There were 2154 time to metastasis (TTM) events and 1460 disease-specific survival (DSS) events, which did not include non-prostate cancer-related deaths. Linear regression showed the 5-year MFS associated with 10-year OS, 0.71 (95% confidence interval [CI] 0.50, 0.80) and with 8-year OS 0.83 (95% CI 0.71, 0.88), log hazard ratio [HR] 0.92 (95% CI 0.81, 0.95). Analysis of whether TTM could serve as a surrogate for DSS revealed that 5-year TTM associated with 10-year DSS, 0.78 (95% CI 0.60, 0.85) and with 8-year DSS 0.86 (95% CI 0.75, 0.90), log HR 0.89 (95% CI 0.72,0.93). Xie *et al.* Abstract 717O

Practice point and future research opportunities

Results from this meta-analysis suggest that metastasis-free survival may be used as a surrogate endpoint for OS in clinical trials evaluating patients with localised prostate cancer, and that the time to metastasis may serve as a surrogate end-point of disease-specific survival. Both metastasis-free survival and time to metastasis usually can be measured earlier than overall or disease-specific survival.

Phase II findings show early evidence of anti-PD-1 activity in mCRPC

Julie N. Graff, Knight Cancer Institute, Oregon Health Science University, Portland, USA presented first results from first 14 patients treated with panitumumab added to enzalutamide in an ongoing phase II clinical trial. The study showed for the first time evidence of meaningful clinical activity for PD-1 blockade in men with metastatic prostate cancer that showed resistance to androgen deprivation. In the trial, men with metastatic castration resistant prostate cancer (CRPC) that progressed on the androgen receptor antagonist enzalutamide were treated with pembrolizumab at 200 mg i.v. every 3 weeks for 4 doses with continued enzalutamide. Men having chemotherapy for mCRPC were not enrolled. The primary endpoint of the ongoing trial is the proportion of men with a prostate specific antigen (PSA) response ≥ 50%. The secondary endpoints were objective disease response, PSA progression-free survival, and overall survival.

Following pembrolizumab/enzalutamide treatment, 4 patients experienced rapid, confirmed reductions in PSA≥ 50%, and achieved serum PSA levels less than 0.1 ng/ml. These patients remained progression-free at 9 to up to 54 weeks of treatment. Stable disease was seen in 6

patients, and 4 patients experienced progressive disease.

Subsequent imaging scans taken in 2 of the 4 responders with measurable disease in the liver and lymph nodes showed tumour shrinkage, and both achieved partial response that was durable for 54 and 15 weeks of follow-up. Two responding patients experienced reduction of cancer-related pain that was sufficient to allow discontinuation of opiate pain medication. Biopsies had been taken at baseline, when possible, and protein expression was evaluated by immunohistochemistry. This analysis revealed the presence of CD3+, CD8+, and CD163+ leukocyte infiltrates, and PD-L1 expression in 2 of the responder's samples.

Significant immune-related adverse events were reported in 4 patients, including grade 2 myositis with muscle weakness and pain, grade 3 hypothyroidism, and grade 2 hypothyroidism. NCT02312557. Graff *et al.* Abstract 719O

Practice point and future research opportunities

Early results from this trial of pembrolizumab in metastatic prostate cancer demonstrate profound, ongoing responses to PD-1 inhibition with pembrolizumab plus enzalutamide in some men with mCRPC. Approved agents for mCRPC rarely produce PSA reduction to less than 0.2 ng/ml after enzalutamide has stopped working. Significant responses in liver metastases are also relatively uncommon with androgen receptor-targeting drugs or cytotoxic chemotherapies. These promising results represent the experience of the first 14 patients treated with pembrolizumab and must be viewed as preliminary. The ongoing study, which is continuing to follow these men and has enrolled additional participants, will provide more robust answers about the potential benefits of PD-1 inhibition for men with metastatic prostate cancer.

GENITOURINARY TUMOURS - nonPROSTATE

Sunitinib shows promise as adjuvant treatment in post-nephrectomy high-risk RCC

Lead author Alain Ravaud of the Hôpital Saint-André in Bordeaux, France discussed findings from the S-TRAC phase III study that randomised 309 treatment-naive patients with locoregional renal cell carcinoma (RCC) to receive sunitinib and 306 patients to receive placebo. The study included patients that had undergone nephrectomy that were at high-risk but with no evidence of metastasis upon central review of imaging done at baseline. Patients were started on 50 mg/day of sunitinib orally for 4 weeks on/2 weeks off or on placebo for the same schedule. Sunitinib dose reductions to a minimum of 37.5 mg/day were allowed. In the sunitinib cohort, the median number of cycles was 9 and relative dose intensity was 88.4%. Both treatment arms were well balanced at baseline for demographic and disease characteristics.

Sunitinib extended disease-free survival (DFS), the primary endpoint, to 6.8 years (95% confidence interval [CI] 5.8, NR) versus 5.6 years (95% CI 3.8, 6.6) years with placebo, by blinded independent review, hazard ratio [HR] 0.76; (p = 0.030). Fewer DFS events were seen with sunitinib; 113 DFS events occurred in 36.6% of patients versus 144 events in 47.1% of placebo patients.

Analyses of a subgroup of higher risk patients supported these findings; DFS in this subgroup was 6.2 years versus 4.0 years with placebo, HR 0.76 (p = 0.044). OS data were immature at data cut-off. The rate of serious adverse events (grade 3 or higher) was 63.4% in the sunitinib arm and 21.7% in the placebo arm. These results were published simultaneously online in *The New England Journal of Medicine (NEJM)*. NCT00375674. Ravaud *et al.* Abstract LBA11_PR; *NEJM* 2016; 375:2246-2254.

Practice point and future research opportunities

The recurrence rate following nephrectomy distinguishes RCC from other tumours that have a lower risk of recurrence. Approximately 16% of all cases of RCC are diagnosed with locoregional disease, and of these, up to 49% have a relapse with metastasis after nephrectomy, making a strong argument for adjuvant therapy. These are the first positive data in the adjuvant setting in loco-regional RCC and the result of this trial could change practice, if approved by health authorities, because there is currently no standard adjuvant treatment for clear-cell RCC. Sunitinib is a potential new option for adjuvant therapy in these patients, given the increase in DFS and the manageable safety profile.

An important caution is that the results apply to only the patient population represented in the trial: patients with clear-cell, high-risk RCC without metastases, and that sunitinib should be given at a starting dose of 50 mg with dose reductions to 37.5 mg/day, as in this study. A different regimen of adjuvant sunitinib was administered in the ASSURE trial, which showed no difference in DFS or OS. These contradictory findings generate uncertainty. Also, DFS is a useful surrogate

endpoint, but does not necessarily translate to OS, which is the gold standard. There are a number of other trials ongoing in this area and additional positive data could tip the balance towards recommending sunitinib as adjuvant therapy.

First-line cabozantinib improves PFS over sunitinib in mRCC

Toni Choueiri, director of the Lank Centre for Genitourinary Oncology at the Dana-Farber Cancer Institute in Boston, USA presented findings on behalf of colleagues from the phase II multicentre trial wherein 157 patients with untreated clear-cell metastatic renal cell carcinoma (mRCC) of intermediate or poor risk, and ECOG performance status 0 to 2, were randomised 1:1 to oral cabozantinib at 60 mg once daily or sunitinib at 50 mg once daily, 4 weeks on, 2 weeks off. The International mRCC Database Consortium Criteria (IMDC) intermediate risk was reported for 80.9% of patients, and 36.3% had bone metastases; these patients were equally distributed across treatment arms.

After a median follow up of 20.8 months patients treated with cabozantinib showed a 31% reduction in the rate of progression or death compared to those treated with sunitinib, adjusted hazard ratio HR [0.69]; 95% confidence interval [CI] 0.48, 0.98 (one-sided p = 0.012). The median progression-free survival (PFS) was 8.2 months, (95% CI 6.2, 8.8) compared to 5.6 months (95% CI 95% 3.4, 8.2), respectively (p = 0.012). The objective response rate was also significantly higher at 46% (95% CI 34, 57%) in the cabozantinib arm compared to 18% (95% CI 10-28%) in the sunitinib arm. Median overall survival was 26.4 months with cabozantinib compared to 23.5 months with sunitinib (adjusted HR 0.87, 95% CI 0.55, 1.4). At data cut-off, 13 (16.46%) cabozantinib patients versus 2 (2.56%) sunitinib patients remained on treatment.

Investigators observed a similar rate of adverse events (AEs) between the two arms of the study; the incidence of grade 3 or higher AEs was 70.5% in the cabozantinib arm and 72.2% in the sunitinib arm. The most common AEs for both treatments included diarrhoea, fatigue, hypertension, palmar-plantar erythrodysesthesia. Haematological events were higher with sunitinib; haematological events were reported in 2.6% of cabozantinib versus 22.2% of sunitinib patients. Treatment was terminated early due to toxicity by 16 patients in each arm. NCT01835158. Choueiri *et al.* Abstract LBA30_PR

Practice point and future research opportunities

In this trial, cabozantinib demonstrated a significant benefit in both PFS and ORR over standard sunitinib in poor-risk patients with untreated intermediate mRCC. Sunitinib targets the vascular endothelial growth factor receptor (VEGFR) but cabozantinib inhibits a broader range of activity, including VEGFR2, MET and AXL activity, and has demonstrated clinical benefit following anti-VEGFR therapy. Both MET and AXL seem to be associated with tumour progression, but more importantly, animal models showed that the development of resistance to VEGFR inhibitors like sunitinib can be mediated through AXL and MET. It is unknown whether these results are expandable to all mRCC patients, including patients with a good prognosis. The study did not include good-risk patients, but there is no biological or clinical rationale to think that cabozantinib would not be equally effective in that population. While more mature data and additional studies using cabozantinib in the first line setting will be required, this study raises

new expectations for the first-line treatment of mRCC.

For many years, sunitinib has been the most commonly used standard of care in first-line mRCC, and recently, cabozantinib demonstrated activity in second line for these patients, especially after sunitinib failure. Cabozantinib is currently approved for second or later lines of treatment in patients that have progressed on a VEGFR tyrosine kinase inhibitor, but these data show that cabozantinib has the potential to become a first-line standard treatment in mRCC.

Nivolumab in second line treatment of metastatic urothelial cancer

Lead author Matthew Galsky, Mount Sinai School of Medicine, New York, USA presented safety and efficacy findings on behalf of colleagues from the phase II CheckMate 275 trial. The investigators conducted this open-label, single-arm, phase II study in 270 patients with metastatic urothelial cancer who progressed despite first line platinum-based chemotherapy and who received nivolumab at 3 mg/kg i.v every 2 weeks until progression or unacceptable toxicity. The patients' median age was 66 years and 84.1% of patients had visceral metastases at baseline. Overall, 42.2% of patients had received one, and 29.3% of patients underwent 2 or more prior treatment regimens in the metastatic setting. The primary endpoint was objective response rate (ORR) by RECIST 1.1 confirmed by blinded independent review committee.

CheckMate 275 is the largest study of a PD-1 inhibitor in bladder cancer reported to date and showed a rapid response to nivolumab. The medium time to response was 1.9 (range: 1.8 to 5.9) months. The median duration of response has not yet been reached, but responses at a median follow-up of 7 months are ongoing in 76.9% of responders, and 24.4% of 265 patients remained on therapy. Median progression-free survival (PFS) in the overall cohort was 2 months (95% confidence interval [CI] 1.87, 2.63); median PFS was 1.87 in patients having less than 1% PD-L1 expression and increased to 3.55 months in patients with PD-L1 expression of 1% or greater.

Median overall survival (OS) was 8.74 months (95% CI 6.05, not estimable); median OS was 5.95 months in patients having less than 1% PD-L1 expression and 11.3 months in patients with PD-L1 expression of 1% or greater. Although higher PD-L1 expression was associated with a higher ORR of 19.6%, patients with low to no PD-L1 expression also responded well to nivolumab and demonstrated an ORR of 16.1%.

Biomarker analysis was done by immunohistochemistry to determine the association between response, urothelial cancer subtype (by The Cancer Genome Atlas), and immune gene signature expression. PD-L1 expression ≥1% and ≥5% was reported for 45.9% and 30.7% of patients, respectively. Biomarker analyses showed that the strongest nivolumab response was associated with basal 1 (ORR 69.5%), and luminal 2 (ORR 66.3%) subtypes. The basal 1 subtype also showed the strongest interferonγ gene signature expression.

A total of 18% of patients experienced grade 3/4 treatment-related adverse events (TRAEs); fatigue and diarrhoea were the most frequently reported and each occurred in 2% of patients. Grade 5 adverse events consisted of one death each due to cardiovascular disease, pneumonitis, and acute respiratory failure. Treatment discontinuation due to a TRAE grade 3/4 was reported for 3 patients. Quality of life, as assessed using the Global Health Status Scale, improved from baseline and remained stable over the course of the trial. NCT02387996. Galsky *et al.* Abstract LBA31_PR

Practice point and future research opportunities

The majority of patients with metastatic urothelial cancer experience disease progression despite platinum-based chemotherapy and there are limited treatment options for these patients. Immune checkpoint blockade has become the most promising approach fin this setting. Nivolumab previously demonstrated impressive anti-tumour activity and prolonged overall survival across multiple tumour types. These data are being submitted to support registration of nivolumab as second-line treatment for patients with metastatic urothelial cancer that has progressed despite platinum-based chemotherapy, an indication for which breakthrough therapy designation was granted by the US Food and Drug Administration in June 2016 and the European Medicines Agency initiated review.

Anti-tumour activity with first-line pembrolizumab in advanced/metastatic urothelial cancer

Arjun Balar, NYU Langone Medical Centre in New York, USA presented findings from a preplanned interim analysis of the first 100 patients participating in the KEYNOTE-052 phase II trial of first-line pembrolizumab in cisplatin ineligible patients with metastatic urothelial cancer. KEYNOTE enrolled 374 adult patients with pathologically confirmed and measurable urothelial cancer, and ECOG performance status (PS) 0-2. The patients were cisplatin ineligible due to renal insufficiency in 45% of patients, and ECOG PS 2 plus renal insufficiency in 11% of patients. The patients' median age was 75 (range: 44 to 94) years, 87 (87%) patients had visceral metastases at baseline, and 46% of patients were ECOG PS 2/3. All patients received pembrolizumab at 200 mg every 3 weeks until progressive disease, unacceptable toxicity, or 24 months of treatment. The primary end point was RECIST v1.1 confirmed objective response rate (ORR) by independent review in all patients, and by combined positive score (CPS) in PD-L1–positive patients. The secondary objective was the determination of the CPS-high biomarker cut-point.

The ORR at a median follow-up of 8 months was 24.0% in the overall cohort (95% confidence interval [CI] 16.0, 33.6). Pembrolizumab treatment yielded a rapid response with a median time to response of 2 months (range: 0.1 to 13.4 months). Complete response (CR) was reported for 6 patients and partial response for 17 patients in the overall cohort. Stable disease was reported in 15 (15%) patients and 48 patients experienced progressive disease. The median duration of response (DOR) has not been reached (range: 1.4+ to 9.8+ months). The duration of response (DOR) rate ≥6 months was 83% by Kaplan-Meier estimate. The best change in tumour size was -30% from baseline, by RESIST 1.1, Central Review. A decrease in the target lesion was

reported for 52% of patients. Four patients were non-evaluable and 10 patients were not assessed for response.

When patients were stratified according to a CPS depicting of the level of PD-L1 expression on the tumour and surrounding immune cells, 33 patients with CPS <1 had an ORR of 18%, 33 patients with CPS ≥1% but <10 achieved an ORR of 15%, and 33 patients with CPS ≥10% expression levels achieved ORR 37%. The location of both the primary tumour and metastases were found to also affect pembrolizumab activity. Patients with a primary tumour in the upper tract had an ORR of 10% whereas patients with lower tract disease had an ORR of 28%. Regarding metastasis location, the ORR was 40% in 10 patients having lymph node involvement only, compared to ORR of 21% in 87 patients with visceral disease.

Pembrolizumab was well tolerated, with 67% of patients experiencing a drug-related adverse event (DRAE). The most common DRAE reported by 14% of patients was fatigue. A grade 3/4 DRAE occurred in 16% of patients and 5 patients discontinued therapy due to a DRAE. This trial is ongoing and pembrolizumab is being investigated as first-line treatment for advanced urothelial cancer in the phase III KEYNOTE-361 study. NCT02335424. Balar *et al.* Abstract LBA32_PR

Practice point and future research opportunities

Pembrolizumab administered in the first-line demonstrated substantial antitumour activity and favourable safety profile in cisplatin-ineligible patients with advanced/metastatic urothelial cancer. Cisplatin-based chemotherapy is the standard first-line treatment in advanced urothelial cancer but patients with impaired renal function, poor PS, and comorbidities, such as hearing loss, neuropathy, or heart failure are not eligible for this treatment. These patients are generally treated with a gemcitabine and carboplatin combination, which is associated with a 36% response rate; however, there is substantial toxicity and 21% of patients discontinue treatment due to toxicity,

Pembrolizumab treated patients demonstrated a 24% response rate that became greater as expression levels of PD-L1 on the tumour and surrounding immune cells increased. A PD-L1 high cut point of CPS ≥10% seems to identify patients most likely to respond well to pembrolizumab. This biomarker cut point is being validated in the study population in the ongoing trial.

GYNAECOLOGICAL CANCER

Niraparib in second-line treatment for platinum sensitive recurrant ovarian cancer

Niraparib, a novel PARP inhibitor, significantly improved the outcome of patients with platinum-sensitive recurrent ovarian cancer and may provide a sorely needed treatment option in this setting. The current standard, platinum-based chemotherapy is limited by cumulative toxicity and a lack of additional benefit with time, which generally results in a treatment pause until the next relapse, according to Mansoor Raza Mirza, Rigshospitalet, Copenhagen University Hospital, Denmark and medical director of the Nordic Society of Gynaecological Oncology (NSGO). Professor Mirza and colleagues in the European Network of Gynaecological Oncology Trial groups (ENGOT) conducted the phase III ENGOT-OV16/NOVA trial to assess the efficacy and safety of niraparib as maintenance therapy in 553 patients with recurrent ovarian cancer that also were responsive to platinum-based chemotherapy. Baseline testing showed 203 patients had germline BRCA mutation and 350 did not; the patients were stratified by BRCA mutation status and randomised 2:1 to receive niraparib at 300 mg or placebo once daily.

The trial met its primary endpoint of progression-free survival (PFS), with niraparib considerably prolonging PFS compared to placebo across all patient cohorts. Median PFS with niraparib was 21.0 months compared to 5.5 months with placebo in patients with germline BRCA mutation, hazard ratio [HR] 0.27; 95% confidence interval [CI] 0.173, 0.410 ($p < 0.0001$). PFS was shorter but prolonged over placebo in patients without baseline BRCA mutation who demonstrated median PFS of 9.3 months versus 3.9 months with niraparib versus placebo, respectively, HR 0.45; 95% CI 0.338, 0.607 ($p < 0.0001$). Median PFS was12.9 versus 3.8 months in a subgroup of patients without BRAF mutation but with homologous recombination DNA repair deficiencies, HR 0.38; 95% CI 0.243, 0.586 ($p < 0.0001$). Significant improvements were also observed in all secondary endpoints. Compared to placebo, niraparib significantly prolonged the second PFS, time to first subsequent treatment, and chemotherapy-free interval in all 3 patient populations.

Grade 3/4 adverse event with niraparib included 28% of patients with thrombocytopenia, 25% had anaemia, and 11% of patients had neutropenia. These were resolved with dose adjustments and patients could continue their treatment. Patient-reported outcomes were similar with niraparib and placebo. Patients on niraparib maintained symptom control and had a quality of life comparable to those on placebo. These findings were published simultaneously online in *The New England Journal of Medicine (NEJM)*. NCT01847274. Mizra *et al.* Abstract LBA3_PR; *NEJM* 2016; 375:2154-2164.

Practice point and future research opportunities

The current options for maintenance therapy in the EU are bevacizumab, which can only be given once and improves PFS by just a few months, and the PARP inhibitor olaparib, which is only approved in patients with a germline BRCA mutation (about 10–15% of ovarian cancer patients). No maintenance therapy is approved outside the EU. The results from this study more than doubles the population of patients who may benefit from a PARP inhibitor; niraparib demonstrated large benefits in PFS in recurrent ovarian cancer. These landmark results could

change the way this disease is treated. That PARP inhibitors benefit patients with BRCA mutations has been demonstrated but niraparib seems to benefit patients with recurrent ovarian cancer who respond to platinum regardless of BRCA status.

This study was also the first trial to demonstrate that using homologous recombination deficiency to select patients for treatment is a useful strategy. Future studies are needed to define responder and non-responders to this treatment.

Low response rates halt CORAL study of abiraterone in patients with recurrent epithelial ovarian cancer

Susanna Banerjee, Royal Marsden NHS Foundation Trust, London, UK presented results from the CORAL phase II trial which evaluated the efficacy of abiraterone in patients with ovarian cancer. Dr. Banerjee and colleagues conducted the CORAL phase II trial in 42 patients with epithelial ovarian cancer who had progressed within 12 months of the last systemic therapy. The patients had a median age of 64 (range: 34 to 85) years, and 88% had high-grade serous histology. The patients had not received prior hormonal anticancer agents, but 47% had received 3 or more previous lines of therapy. The median time from diagnosis was 2.8 years. All patients were administered abiraterone acetate at 1,000 mg plus 5 mg prednisone daily until disease progression or end of study. Tissue and blood samples were obtained for determination of hormone receptor status; at baseline, 29 (69%) patients were positive for androgen receptor (AR) expression, 35 (83.3%) were positive for the oestrogen receptor (ER), and 25 (59.5%) patients were positive for the progesterone receptor (PgR). The primary endpoint of CORAL was the overall response rate (ORR) according to combined RECIST at 12 weeks, and the secondary endpoint was the clinical benefit rate (CBR) at 12 weeks.

CORAL, the first trial of abiraterone in ovarian cancer was halted early due to low response. At 12 weeks, the response rate was 2.4% in the overall study cohort and 3.4% in patients expressing the AR. However, one patient achieved complete response (CR). This patient was AR positive and had low-grade serous histology, achieved a CR that lasted for 47 weeks, and remains on abiraterone. A total of 11 patients showed clinical benefit at 12 weeks, which was prolonged to 24 weeks for 4 patients.

Treatment emergent adverse events (TEAEs) grade 3/4 included hypertension in 29% of patients, and hypokalaemia in 10%. Dose delays were required in 23% of patients lasting for an average of 7.6 days. Treatment discontinuation due to disease progression was reported for 78% of patients, 3 patients also choose to discontinue treatment, and 3 discontinuations occurred for other reasons. The investigators are assessing why some patients had clinical benefit by analysing their tumour and blood samples. EudraCT Number: 2013-000293-29 (17-01-2013). Banerjee *et al.* Abstract LBA33_PR

Practice point and future research opportunities

Abiraterone is a CYP17 inhibitor of androgen biosynthesis approved for the androgen deprivation treatment of prostate cancer; therefore, it should decrease androgen binding to the AR, which is reported to be expressed in up to 90% of epithelial ovarian cancer cases. Although the CORAL trial did not reach the desired level of activity, leading to early trial closure, some patients did respond, including one CR. There remains an urgent need to develop smarter treatment options for women with recurrent epithelial ovarian cancer

Further investigation of the role of the AR pathway in epithelial ovarian cancer may warrant further investigation.

Use of a novel oncologist-led BRCA1/2 germline mutation testing and counselling model for patients with ovarian cancer yields high marks for patient and clinician satisfaction

Giovanni Scambia, Gynaecology Oncology, Policlinico Universitario A. Gemelli Università Cattolica del Sacro Cuore, Rome, Italy, and colleague conducted ENGAGE, the first real-world study to evaluate whether an oncologist-led testing model first used at the Institute of Cancer Research and Royal Marsden Hospital, London, UK facilitates germline BRCA mutation (gBRCAm) testing and genetic counselling. ENGAGE is an ongoing prospective, observational study that was conducted across 11 sites in the US, 8 in Italy, and 7 sites in Spain, and enrolled 710 adult patients with epithelial ovarian, fallopian tube or primary peritoneal cancer. The analysis included baseline demographic, clinical and therapeutic data, and primary outcome data, including gBRCAm testing turnaround time, outcome of the BRCA test, and surveys completed by patients and oncogenetic counsellors regarding satisfaction with the model.

Professor Scambia reported findings from an interim analysis that comprised data from 444 patients with mean (standard deviation) age 63.7 (10.6) years. The median time since diagnosis was 0.8 years, 38% of participants were newly diagnosed, and 38% had family history of breast or ovarian cancer. Pre-BRCA test counselling was provided by oncologists (40%) or nurses (56%) in the US and by oncologists in Europe. Only one patient requested additional pre-test counselling. Mean (standard deviation) turnaround time from initial counselling to receipt of BRCA test results or oncogenetic counselling overall was 6.7 (SD 4.5) weeks. In the US, turnaround time was 5.1 (SD 3.7) weeks and 10.0 (SD 4.2) weeks in the EU. BRCA testing was performed in a central laboratory in 91% of cases. BRCA mutation was identified in 10% of patients. Mean patient-reported fulfilment of expectations and overall satisfaction with counselling were both >3.7/4 pre-/post-BRCA testing. Most patients, 92%, were satisfied to have the genetic test at an existing rather than a separate visit. Over 80% of oncologists reported that the BRCA-testing process worked well and that counselling patients on BRCA testing was an efficient use of their time. NCT02406235. Scambia *et al.* Abstract LBA34

Practice point and future research opportunities

Findings from this interim analysis support the novel testing model, which facilitated genetic counselling and provided the potential for quicker treatment decisions and better use of

resources. The model resulted in reduced turnaround times and high acceptance and satisfaction levels were reported by both patients and staff.

Single-agent selinexor shows promise in heavily pre-treated gynaecological cancers

Selinexor is a first-in-class inhibitor of XPO1, a nuclear export protein that is expressed in aggressive ovarian cancers and is also commonly expressed in patients with endometrial cancer. XPO1 has been linked to poorer patient outcomes. Ignace B. Vergote, Department of obstetrics and gynaecology and of gynaecologic oncology, Catholic University of Leuven in Belgium, and colleagues evaluated the safety and efficacy of selinexor in a phase II trial in 66 patients with ovarian cancer, 23 patients with endometrial cancer and 25 patients with cervical cancer. Patients in the respective groups, had received a median number of 6 (range: 1 to 11), 2 (range: 1 to 5), and 3 (range: 1 to 8) prior treatment regimens. All patients with ovarian cancer were refractory to platinum chemotherapy, and all patients with endometrial and cervical cancers had received at least one prior line of chemotherapy. Patients with ovarian cancer were randomly assigned to one of treatment schedules: selinexor at 50 mg/m^2 twice weekly, 35 mg/m^2 twice weekly, or 50 mg/m^2 every week in 4-week cycles. All other patients received selinexor 50 mg/m^2 twice weekly. The primary endpoint of the study was disease control rate (DCR) at week 12 and secondary endpoints included overall response rate (ORR), progression-free survival (PFS), duration of response (DoR), safety and tolerability.

At 12 weeks the DCR was 49% in patients with ovarian cancer across dosing schedules, and patients with endometrial cancer demonstrated a DCR of 45%: however, the DCR was 6% in patients with cervical cancer. The ORR was 14% among both patients with ovarian cancer, 15% among patients with endometrial cancer, and 4% in patients with cervical cancer. Across all parametres, selinexor demonstrated clinical benefit that was much lower in the cervical cancer cohort. Median PFS was 3 months among patients with ovarian and endometrial cancers, versus one month in patients with cervical cancer. Median overall survival was 7 months in patients with ovarian cancer, 8 months in patients with endometrial cancer and 5 months in patients with cervical cancer.

Analysis of the patients' blood samples for circulating tumour cells (CTCs) showed that patients with CTCs prior to treatment tended to have shorter PFS.

Common grade 1 and grade 2 drug-related adverse events (AEs) that occurred in all patients included nausea (56%), anorexia (47%), weight loss (44%) and fatigue (42%). Grade 3 drug-related AEs included thrombocytopenia (11%), fatigue (10%), anaemia (9%) and nausea (8%). One patient each experienced grade 4 cataract and hyponatremia. Based on these results, phase III trials are planned to evaluate selinexor in patients with ovarian and endometrial cancers. EduraCT No: 2013-003650-24; Clinical Trials NCT02025985. Vergote *et al.* Abstract 854O

Practice point and future research opportunities

Single-agent selinexor demonstrated interesting antitumour activity in heavily pretreated ovarian and endometrial cancers, but showed far less activity in patients with cervical cancer. It is surprising that the worst disease control rate was seen in patients with cervical cancer, despite the fact that this is an HPV–induced tumour, where a greater response than in the two other cohorts could have been expected. Selinexor offers promise as new treatment for heavily pretreated ovarian and endometrial cancers that warrants phase III confirmation.

Novel CHK1/2 inhibitor demonstrates activity in patients with sporadic high-grade serous ovarian cancer and germline BRCA mutation-associated ovarian cancer

Lead author Jung-Min Lee, Women's Malignancies Branch, National Cancer Institute, Rockville, USA and colleagues reasoned that LY2606368 could have clinical activity in high-grade serous ovarian cancer (HGSOC). LY2606368 is a second-generation inhibitor of checkpoint kinases 1/2 (CHK1/2), which are the primary cell cycle regulators in tumours with p53 dysfunction, including HGSOC. The study of LY2606368 enrolled 15 women with recurrent HGSOC plus negative BRCA testing or a negative family history of hereditary breast and ovarian cancer syndrome (cohort 1) and 7 women with a documented deleterious germline BRCA1/2 mutation (cohort 2). All patients had good end organ function, ECOG performance status 0-2, and disease that could be safely biopsied. The median age was 61 (range: 36 to 83) years. The median number of prior therapies was 5 (range: 1 to 13) in cohort 1 and 7 (range: 3 to 12) in cohort 2. All patients were treated with LY2606368 at 105 mg/m^2 i.v. every 14 days per 28-day cycle. Response was assessed every 2 cycles by RECIST v1.1, and safety by CTCAE v4.0 per cycle. The primary endpoint was overall response rate (ORR).

The ORR in 13 evaluable patients in cohort 1 was 38% with 5 patients achieving partial response (PR). The median duration of response (DoR) was 9 months (range: 3 plus to 9 plus months); 2 of the responding patients had platinum-sensitive and 3 had platinum-resistant disease. In cohort 2, stable disease lasting 4 or more months was attained by 4 of 6 evaluable patients (median DoR was 4.5 months), but there were no responses. Grade 3 or 4 treatment-emergent adverse events (AEs) included neutropenia in 91% of patients, thrombocytopenia in 27%, febrile neutropenia in 9%, and diarrhoea in 9% of patients. Grade 3 or 4 neutropenia occurring on day 8 resolved within 7 days in 13 patients and 13 patients received growth factor support due to febrile neutropenia or to avoid treatment delays. This study continues to enroll patients and paired tumour biopsy and blood samples are being collected to examine potential biomarkers of response. NCT02203513. Lee *et al.* Abstract 855O

Practice point and future research opportunities

In this study, the novel second-generation inhibitor of CHK½, LY2606368 administered as sole treatment in patients with BRCA wild-type high-grade serous ovarian cancer showed promising preliminary activity. Prophylactic use of G-CSF should be considered with this agent.

HAEMATOLOGICAL MALIGNANCIES

Phase III results from the CASTOR trial of daratumumab, bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma

Katja Weisel, Universitaetsklinikum Tuebingen der Eberhard-Karls-Universitaet, Abteilung fuer Innere Medizin II, Tuebingen, Germany presented findings from CASTOR, a randomised phase III trial of combined daratumumab, bortezomib, and dexamethasone treatment versus bortezomib and dexamethasone. The CASTOR enrolled 498 patients with relapsed or refractory multiple myeloma who had received a median of 2 prior lines of therapy (range: 1 to 10); 66% of patients had received prior bortezomib, 76% received prior immunomodulatory drugs, and 48% had received prior proteasome inhibitors and immunomodulatory drugs. Patients in the trial were treated with 8 cycles of bortezomib/dexamethasone with or without 16 mg/kg of daratumumab. Bortezomib was administered subcutaneously at 1.3 mg/m2 on days 1, 4, 8, and 11 of each 21-day cycle for a maximum of 8 cycles. Patients received 20 mg of oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12 of the first 8 bortezomib treatment cycles. Patients in the daratumumab group received an intravenous infusion of daratumumab at 16 mg/kg weekly for the first 3 cycles, on day 1 of cycles 4 to 9, and then every 4 weeks.

The primary endpoint was progression-free survival (PFS) and secondary endpoints include time-to-progression (TTP), objective response rate (ORR), overall survival (OS), and safety.

The 12-month PFS rate was 60.7% in patients receiving the triple combination of daratumumab, bortezomib, and dexamethasone versus 26.9% in patients receiving bortezomib and dexamethasone. After a median follow-up period of 7.4 months, the median PFS was not reached in the daratumumab group versus 7.2 months in the control group, hazard ratio [HR] 0.39; 95% confidence interval [CI] 0.28, 0.53 ($p < 0.0001$). Partial response was attained by 59.2% of daratumumab patients versus 29.1% of control patients ($p < 0.001$) and complete response was achieved by 19.2% versus 9.0% of patients receiving daratumumab versus control, respectively ($p = 0.001$). The ORR was also higher with the addition of daratumumab at 82.9% compared with 63.2% in the control group ($p < 0.001$). After meeting its primary endpoint for PFS, the CASTOR study was halted to allow patients in the control arm to cross over to receive daratumumab.

The most commonly reported grade 3 or 4 adverse events (AEs) in patients treated with daratumumab in combination with bortezomib and dexamethasone compared with those who only received bortezomib and dexamethasone were thrombocytopenia (45.3% versus 32.9%), anaemia (14.4% versus 16.0%), and neutropenia (12.8% versus 4.2%). Daratumumab-associated infusion-related reactions were reported in 45.3% of patients, were mostly grade 1/2, and occurred mainly during the first infusion, which is consistent with the previously reported safety profile of daratumumab monotherapy and background bortezomib/dexamethasone therapy. These findings have been published in *The New England Journal of Medicine*. NCT02136134. Weisel *et al.* Abstract 906O

Practice point and future research opportunities

Daratumumab is the first CD38–targeting monoclonal antibody approved for multiple myeloma; in November 2015, daratumumab was granted an accelerated approval by the FDA as a monotherapy for patients with multiple myeloma who had undergone 3 or more prior therapies based on data from 2 open-label clinical trials. The CASTOR study served as one of the confirmatory trials required for full approval. In this trial, daratumumab significantly improved PFS when added to bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma. These data formed part of the basis of submission of the supplemental Biologics License Application to the US Food and Drug Administration and the submission of the variation to the Marketing Authorisation to the European Medicines Agency for daratumumab. Longer patient follow-up is planned to determine the impact of the daratumumab combination on OS.

Prophylaxis with high-dose methotrexate is highly effective in preventing CNS recurrence in patients with high-risk DLBCL

Theresa Calimeri and colleagues at the IRCCS San Raffaele in Milan, Italy conducted a retrospective analysis that evaluated central nervous system (CNS) prophylaxis in 242 patients with diffuse large B-cell lymphoma (DLBCL) to prevent CNS dissemination. Data from consecutive HIV-negative adults with DLBCL who were treated with first-line R-CHOP or similar chemotherapy with and without radiotherapy were included. The risk of CNS dissemination was based on involvement of specific extranodal organs, including the testis, kidney/adrenal, spine, skull, paranasal sinuses, orbit, and/or breast and/or International Prognostic Index (IPI) of 4-5. Patients diagnosed after 2007 with high CNS recurrence risk received CNS prophylaxis, consisting of 3-4 cycles of methotrexate 3 g/m^2 ± intrathecal chemotherapy (IT). The patients´ median age was 66 (range: 18 to 89) years. The risk of CNS dissemination risk was low in 147 (61%) patients and high in 95 (39%) patients. CNS prophylaxis was indicated for 47 high-risk patients; of these, 36 received high dose methotrexate with or without IT and 11 patients received only IT due to MTHFR polymorphisms, comorbidity or old age.

At follow-up of a median 51 months (range: 12 to171 months), the CNS relapse rate was less than 1%, which represented one patient in the low-risk cohort versus 10 (11%) in the high-risk cohort. CNS relapse was reported in 11 (4.5%) and 8 of these died of CNS progressive disease after a median of 12 months (range: 7 to 37 months). In the high-risk subgroup, the CNS relapse rate was 17% in patients not receiving CNS prophylaxis versus 18% in patients receiving IT alone, and 0% in high risk patients that received CNS prophylaxis consisting of high-dose methotrexate ± IT (p = 0.004). Overall, 38 high-risk patients experienced relapse, and the CNS was the most common involved site in 10 patients. Survival was significantly improved with CNS prophylaxis; the 3-year progression-free survival rate was 81% versus 46% (p = 0.001) and the 3-year overall survival rate was 86% versus 48% (p = 0.00005) in patients receiving and not receiving prophylactic treatment, respectively. Survival rates were independent of IPI score and extranodal sites. NCT0059731. Claimeri *et al.* Abstract 908O

Practice point and future research opportunities

Prophylaxis with high-dose methotrexate was highly effective in preventing CNS disease recurrence in patients with high-risk diffuse large B-cell lymphoma who were at increased risk of CNS recurrence.

HEAD AND NECK CANCER

Patients with recurrent or metastatic HNSCC maintain function following nivolumab treatment

Kevin Harrington, Division of Radiotherapy and Imaging, Institute of Cancer Research, London, UK and The Royal Marsden NHS Foundation Trust presented the results of patient reported outcomes from the CheckMate 141 randomised, open label phase III trial. In this study, 361 patients with platinum refractory relapsed head and neck cancer received nivolumab or standard of care chemotherapy (physician's choice of methotrexate, docetaxel or cetuximab). Previously reported findings demonstrated that overall survival (OS) was improved by an average of 2.5 months with nivolumab over chemotherapy. The patient reported outcomes discussed at ESMO 2016 included functional capacity and physical symptoms following nivolumab or chemotherapy. The European Organisation for Research and Treatment of Cancer QoL Questionnaire (EORTC QLQ-C30), EORTC Head and Neck Cancer module (QLQ-H&N35), and EQ-5D were administered to 129 patients at baseline, 9 weeks, and at 6-week intervals thereafter. An overall score was calculated for global health from questions covering functional areas, such as the physical ability to perform daily activities, and emotional, cognitive, and social aspects of the patients' lives. A score change or difference of 10 points in the EORTC subscales was regarded as clinically relevant.

Patients receiving nivolumab maintained or improved function and symptom burden at 9 and 15 weeks compared to baseline. In contrast, patients receiving standard of care showed poorer scores across all parametres at both time-points compared to baseline. When the scores between the two arms were compared at 9 and 15 weeks, it emerged that nivolumab provided a clinically significant benefit over chemotherapy in most of the function and symptom areas: Time to deterioration was significantly delayed with nivolumab ($p < 0.05$, 2-tailed) compared to chemotherapy regarding global health, physical role, cognitive, and social functioning, and for physical symptoms including fatigue, dyspnoea, and insomnia, as reported on the EORTC QLQ-C30, as well as pain, sensory problems, and mouth opening problems as reported on the QLQ-H&N35. These findings have been published simultaneously in *The New England Journal of Medicine (NEJM).* NCT02105636. Harrington *et al.* Abstract LBA4; *NEJM* 2016; 375:1856-1867.

Practice point and future research opportunities

The historical median survival is 6 months or less in patients with platinum refractory relapsed head and neck cancer. Previously reported findings from this trial showed that nivolumab improved OS by an average of 2.5 months over physician's choice of standard of care chemotherapy. This study assessed symptoms and quality of life using several questionnaires, including one specifically designed for patients with head and neck cancer, which is important because these tumours have specific consequences. For example, a tumour mass in the neck is painful and may impair eating and speaking functions and is also visible and can lead to social isolation. Patient reported outcomes form this trial show that, while prolonging survival, nivolumab also enables patients to function at work and socially, and to experience less pain and fatigue than chemotherapy. These data suggest that the superior clinical activity of

nivolumab maintains patient-reported outcomes, but it is also likely that nivolumab is a gentler treatment that is associated with fewer side effects.

This is the first study to show that an immunotherapy is superior to classical treatment options for improving quality of life and symptoms, on top of prolonging survival. Nivolumab works in around one-third of patients with advanced head and neck cancer and biomarkers or biological criteria are needed to identify patients likely to benefit. When these patients are identified, it can be explained to them that nivolumab may help them to feel and function better in daily life.

Meta analysis confirms superiority of concomitant over induction chemotherapy in non-metastatic HNSCC

Jean Bourhis of the Département d'oncologie, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland presented an update of the MACH-NC meta-analysis on behalf of first author Pierre Blanchard, Department of Radiation Therapy, Gustave Roussy Cancer Campus in Villejuif, France and the MACH-NC group, which confirmed that concomitant chemotherapy added to loco-regional treatment significantly prolongs overall survival (OS) in patients with head and neck squamous cell carcinoma (HNSCC). The investigators analysed individual patient data from 15 new trials in addition to updated patient data from 11 additional trials done between 1965 and 2010 in patients with non-metastatic HNSCC; induction chemotherapy plus radiotherapy was compared to radiotherapy plus concomitant (or alternating) chemotherapy in 2574 patients, and loco-regional treatment (LRT) was compared to LRT plus chemotherapy in 18,394 patients taking part in 94 trials with a median follow-up of 6.7 years. The investigators used a fixed effect model and treatment comparison was evaluated using the log-rank test, stratified by trial. The primary endpoint of the study was OS.

Overall, 29% of patients had stage III tumours and 63% had stage IV tumours. The oropharynx was the most frequently involved tumour site in 35% of patients. Adding chemotherapy to loco-regional therapy significantly improved OS over loco-regional therapy alone, hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.86, 0.92 ($p < 0.0001$). When the chemotherapy was delivered was crucial for this benefit; adding induction chemotherapy did not prolong OS over loco-regional treatment alone, HR 0.97; 95% CI 0.91, 1.03.

The analysis specifically comparing concomitant to induction chemotherapy plus radiotherapy comprised data from 1214 patients participating in 8 trials showed that OS was significantly prolonged with concomitant over induction adjunct chemotherapy, HR 0.84; 95% CI 0.74, 0.95 ($p = 0.007$), and progression-free survival, HR 0.83; 95% CI 0.79, 0.87 ($p < 0.0001$), which translates to a 5- and 10-year absolute survival benefit of 6.5% and 3.4%.). An interaction test done on data from recent trials of concomitant chemotherapy revealed a trend towards decreased efficacy with increasing age and poorer performance status (PS), HR 1.00; 95% CI 0.81, 1.23 (p trend = 0.06) in patients aged 70 or more years, and HR 0.93; 95% CI 0.73, 1.19 (p trend = 0.07) for patients with performance status of 2 or greater. NCT0059731. Blanchard *et al.* Abstract 950O

Practice point and future research opportunities

Findings from this analysis suggest that patients with head and neck squamous cell carcinoma experienced prolonged OS when concomitant chemotherapy was administered with local regional treatment or radiotherapy. This updated meta-analysis, which has a larger cohort and longer patient follow-up, confirmed the superiority of adding concomitant chemotherapy as compared to induction chemotherapy. Patients with head and neck squamous cell carcinoma achieved prolonged overall survival when concomitant chemotherapy was administered with local regional treatment or radiotherapy, However, timing was important, as the survival benefit was not observed with the addition of induction chemotherapy.

Adding motolimod to chemotherapy plus cetuximab in patients with recurrent or metastatic HNSCC fails to improve survival

In order to test whether the efficacy of the EXTREME regimen consisting of platinum, 5-FU, and cetuximab could be enhanced with the addition of motolimod, Enzra Cohen, Translational Science, UCSD Moores Cancer Centre, La Jolla, USA and colleagues conducted the Active8 randomised phase II study. Motolimod is a Toll-like receptor 8 agonist that stimulates the innate immune system and increases antigen-specific T cell responses against EGFR. Motolimod plus cetuximab has been reported to enhance NK cell activity, decrease markers of T cell suppression, and reduce myeloid-derived suppressor cells in tumours. This trial enrolled patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC); 100 patients were randomly assigned to EXTREME plus motolimod and 95 to EXTREME plus placebo. Patients were stratified by ECOG performance status (PS) of 0 versus 1, prior systemic therapy for HNSCC, and choice of cisplatin or carboplatin. The patients had a median age of 58 years (range: 23 to 81), 38% of patients were ECOG PS 0 and 62% ECOG PS 1, and 65% of patients had previously received systemic treatment for HNSCC. At baseline 80% of patients were assigned to receive carboplatin.

The primary endpoint of progression-free survival (PFS) per independent central review was not met. In the intent to treat (ITT) population, the median PFS for EXTREME/motolimod was 185 compared to 181 days with control, hazard ratio [HR] 0.99 (p = 0.266). Median overall survival (OS) was 412 for motolimod versus 343 days for control, HR 0.95 (p = 0.399). However, findings from a subgroup analysis of patients having an injection site reaction (ISR) demonstrated that these patients had significantly improved PFS of 216 versus 181 days, HR 0.69 (p = 0.005), and OS was 570 versus 382 days, HR 0.56 (p = 0.015), respectively with EXTREME/motolimod versus controls. Adverse events occurring more frequently with EXTREME/motolimod included ISR, pyrexia, chills, anaemia, influenza-like illness, and dermatitis acneiform. NCT01836029. Cohen *et al.* Abstract LBA37

Practice point and future research opportunities

Neither PFS nor OS were improved in the ITT population with the addition of motolimod to the EXTREME regimen. Significant survival benefits were observed in a subgroup experiencing immune-related injection site reaction that may warrant further investigation.

PFS and distant metastasis-free survival may serve as surrogate endpoints for OS following chemotherapy in loco-regionally advanced nasopharyngeal carcinoma

Federico Rotolo, Service de Biostatistique et d'Epidemiologie, CESP, Inserm U1018, Universite Paris Sud, and Gustave Roussy Cancer Campus, Villejuif, France and colleagues determined the association of progression-free survival (PFS) and distant metastasis-free survival (DMFS) to overall survival (OS) and evaluated their utility as surrogate endpoints in randomised trials of chemotherapy in loco-regionally advanced nasopharyngeal carcinomas (LANPC). The investigators reviewed individual patient data from 5,144 patients treated in 19 trials contained in the updated Meta-Analysis of Chemotherapy in Nasopharyngeal Carcinoma (MAC-NPC), plus one additional trial. Surrogacy was evaluated at the individual level using a rank correlation coefficient ρ and at the trial level using a correlation coefficient R^2 between treatment effects on the surrogate endpoint and OS.

The analysis revealed a strong association between PFS and OS at both the individual and trial level (ρ = 0.93; 95% confidence interval [CI] 0.93, 0.94) and (R^2 = 0.95; 95% CI 0.47, 1.00), respectively. DMFS also associated with OS on the individual-level (ρ = 0.98; 95% CI 0.98, 0.98): DMFS at trial level could not be computed after the regression was adjusted for measurement error; however, the unadjusted association was high between DMFS and OS (unadjusted R^2 = 0.96; 95% CI 0.94; 0.99).

The sensitivity analysis also showed a strong association between 2-year PFS and 5-year OS at the individual level (ρ = 0.89; 95% CI 0.88,0.90) and at the trial level (R^2 = 0.85, 95% CI 0.46, 1.00). A strong association was also demonstrated between 2-year DMFS and 5-year OS at the individual level (ρ = 0.95; 95% CI 0.94, 0.95) and at the trial level (R^2 = 0.78; 95% CI 0.33,1.00). Rotolo *et al.* Abstract 951O

Practice point and future research opportunities

Both PFS and DMFS showed strong associations with OS in this large meta-analysis, suggesting that both are valid surrogate endpoints for OS when assessing the treatment effect of chemotherapy in loco-regionally advanced nasopharyngeal carcinomas. An additional advantage is that PFS can be measured at an earlier time point.

Comprehensive genomic profiles of metastatic and relapsed salivary gland carcinomas are associated with tumour type and reveal new routes to targeted therapies

Lead author Laurie M. Gay, Pathology, Foundation Medicine, Inc., Cambridge, USA, and colleagues used comprehensive genomic profiling (CGP) to define tumour subtypes of salivary gland tumours, which have diverse histologic subtypes. The investigators also endeavoured to uncover clinically relevant genomic alterations (CRGA), to identify new routes to targeted

therapies for patients with relapsed and metastatic salivary gland carcinomas (SGC). Tumour samples were obtained from 300 consecutive patients with FFPE specimens, from which DNA was extracted. CGP was performed on hybridization-captured, adaptor ligation-based libraries (mean coverage depth >500X) for up to 315 cancer-related genes. The total mutational burden (TMB) was determined on 1.2 Mbp of sequenced DNA. CRGA were defined as genomic alterations targeted by drugs on the market or being evaluated in clinical trials.

Through this genomic testing, the investigators were able to identify specific subtypes of SGC. The most prevalent histologic subtype was acinic cell carcinoma (AiCC) which occurred in 73 patients, followed by adenocarcinoma NOS (Ac-NOS) in 54, muco-epidermoid (MEC) in 48, ductal carcinoma (DCA) in 42, carcinoma NOS (CA-NOS) in 32, adenoid cystic carcinoma (ACC) was identified in 28 patients, and 24 patients had carcinoma ex pleomorphic adenoma (CPA). Mammary associated secretory carcinomas (MASC) were grouped with AC-NOS; AciCC and MEC with ETV-NTRK fusions are likely MASC with unusual histologic presentations.

Non-specialised carcinomas, which includes MEC, DCA, AC-NOS, CA-NOS, and CPA, are frequently ERBB2 driven, but also harbour significant genomic alterations in RET, BRAF and NF1 genes. In these respective subtypes, the mutation frequency of TP53, the gene showing the greatest mutation frequency overall, was 42%, 54%, 53%, 59%, and 46%, respectively. TMB > 10 mutations per Mb was 13% in CA-NOS, 12% in CPA, 11% in DCA, 10% in MEC and 6% and less in the remaining disease subtypes: The investigators determined the opportunity for targeted therapies to be high in DCA, AC-NOS, CA-NOS, and CPA. Modest opportunity was determined for MEC and the opportunity for targeted therapy was low in specialised metastatic SGCs, ACC and AciCC, which had significantly fewer genomic alterations including targetable alterations, as well as less TMB than non-specialised carcinomas. Clinical outcomes following targeted therapies for mSGC were presented. Gay *et al.* Abstract 954PD

Practice point and future research opportunities

Salivary gland carcinomas have a broad diversity of histologic subtypes that have variable clinical aggressiveness and response to local and systemic therapies. Metastatic salivary gland carcinomas include specialised carcinomas, adenoid cystic carcinoma and acinic cell carcinoma, that have low frequencies of genomic alteration, low tumour mutation burden and offer few opportunities for targeted therapies. However, non-specialised salivary gland carcinomas offer more opportunities to use targeted therapies due to more genomic alterations that provide possible treatment targets for HER2, RET, BRAF, and mTOR inhibitors, and also have higher tumour mutation burden, making the use of immune checkpoint inhibitors a possibility.

IMMUNOTHERAPY IN CANCER

Sequencing analysis reveals baseline tumour T cell receptor and neo antigen load associates with sequential nivolumab followed by ipilimumab benefit in melanoma patients

Jeffery S. Weber, the Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, USA presented the results of an analysis of tumour samples obtained pre- and post-treatment in a phase II trial that determined the optimal sequence of immunotherapy with nivolumab and ipilimumab in melanoma. The investigators randomised 140 patients with metastatic unresectable melanoma to be treated with nivolumab followed by ipilimumab with a planned switch at week 12 (arm A), or the reciprocal combination of ipilimumab followed by nivolumab (arm B); both arms received maintenance. In the trial, arm A demonstrated superior best overall response rates and overall survival compared to arm B, while similar safety profiles were observed with each sequence (Weber, J *et al.* Lancet Oncology, 2016).

At ESMO 2016, Dr. Weber presented the results of the analysis done on 94 pre- and post-treatment tumour samples and peripheral blood samples obtained in the trial, which were assessed by DNA sequencing for T cell receptor clonality and the tumours were also analysed for the degree of T cell infiltration. Whole exome sequencing was also performed to assess mutational and neo-epitope load in pre-treatment tumours.

The response to treatment observed in arm A was found to associate with a combination of high T cell fraction and T cell clonality ($p = 0.019$ using Fishers exact test, odds ratio = 6.7), and with survival ($p = 0.05$). However, this association was not seen in arm B. In 22 paired samples, responding patients showed an increase in the tumour T cell fraction and clonality post treatment at week 13 ($p = 0.015$ – signed ranked Wilcox test), whereas tumours from progressing patients showed a decrease in T cell fraction compared to responders' tumours ($p = 0.004$**,** U-test of pooled arms A and B).

In both arms, changes in tumour T cell clonality and T cell fraction were assessed together at week 13, which showed a strong association with response to treatment ($p = 0.0023$; odds ratio 30). Tumour mutational load was also associated with response in the nivolumab then ipilimumab sequence administered in arm A ($p = 0.03$), but not with response in the ipilimumab followed by nivolumab sequence in arm B. Analysis of the peripheral blood revealed no differences in T cell receptor clonality, or the abundance of the top T cell receptor clone post-treatment compared to baseline, peripheral blood pre-treatment T cell receptor parameters did not associate with response to treatment in either arm. NCT01783938. Weber *et al.* Abstract 1047O

Practice point and future research opportunities

Superior response was observed with the sequential administration of nivolumab followed by ipilimumab over the converse sequence. The response from this sequence significantly associated with the tumour micro-environment, degree of T cell infiltration, T cell receptor and clonality at baseline and all were demonstrated to be crucial determinants of the response to this treatment sequence with the PD-1 blocking antibody nivolumab. Altering both parameters may impact on resistance to immunotherapy in melanoma.

ZUMA-1 data demonstrate safety, and feasibility of KTE-C19 anti-CD19 CAR T cells in patients with refractory aggressive B cell NHL

Durable complete responses (CRs) were reported following a single dose of KTE_C19 in patients with non-Hodgkin lymphoma (NHL), according to Frederick L. Locke, Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, USA. Dr. Locke discussed updated findings from the ZUMA-1 phase I-II study of KTE-C19, anti-CD19 chimeric antigen receptor (CAR) T cells. KTE-C19 is an investigational therapy wherein a patient's T cells are genetically modified to express a CAR that is designed to target the antigen CD19, a protein expressed on the cell surface of B-cell lymphomas and leukaemias. ZUMA-1 administered KTE-C19 at a target dose of 2×10^6 anti-CD19 CAR T cells/kg after cyclophosphamide at 500 mg/m^2/day and fludarabine at 30 mg/m^2/day conditioning chemotherapy to 7 patients with refractory aggressive B cell NHL. The patients had ECOG performance status 0-1 and had chemotherapy-refractory disease, which was defined as progressive disease (PD) or stable disease as best response to the last line of therapy, or PD ≤ 12 months after autologous stem cell transplant (ASCT).

The primary objective of the study was the safety of KTE-C19. Secondary objectives included overall response rate (ORR), duration of response, and levels of blood CAR T cells and serum cytokines.

As of April 16, 2016, all 7 patients had received KTE-C19. One patient experienced a dose-limiting toxicity (DLT) of grade 4 encephalopathy and cytokine release syndrome (CRS), and grade 5 intracranial haemorrhage that was determined to be unrelated to KTE-C19. Aside from this patient, all other toxicity related to KTE-C19 of grade ≥3 was resolved.

The ORR was 71%; CR was achieved by 57% of patients and 3 patients experiencing PD within 6 months of ASCT have ongoing CR at 6 to 9 plus months following KTE-C19 therapy. Complete remission was reported for 43% of patients that continued through month 12. The concentration of CAR T cells peaked within two weeks and were detectable from one to 6 months post infusion. This study is ongoing. NCT02348216. Locke *et al.* Abstract 1048O

Practice point and future research opportunities

KTE-C19 utilizes the same CAR construct as the CD28/CD3ζ anti-CD19 CAR T cells that have led to durable remissions in patients with relapsed/refractory B cell malignancies. In this study, a single dose of therapy with the KTE-C19 CAR T cell construct resulted in several CRs that were durable at 12 months and ongoing in patients with refractory aggressive NHL. Cytochrome release syndrome and neurotoxicity were self-limiting and generally reversible. This study

demonstrated that the central manufacturing process and KTE-C19 regimen were safe and feasible for further study. These data support the potential for KTE-C19 to be a breakthrough therapy for chemorefractory, aggressive NHL.

Preventive dendritic cell vaccination is feasible in healthy Lynch syndrome mutation carriers

Colorectal cancer, especially in young individuals, has a link to the Lynch syndrome (LS), an inherited syndrome that is caused by monoallelic germline aberrations affecting one of the DNA mismatch repair (MMR) genes; these defects in the DNA MMR pathway provide the basis for the development of microsatellite instability that is the hallmark of cancer associated with Lynch syndrome, according to Harm Westdorp, Tumour Immunology and Medical Oncology, Radboud University Medical Centre Nijmegen, in Nijmegen, Netherlands. The cumulative risk of colorectal cancer varies between 10 to 80% and is strongly associated with the causative germline defect. MMR deficiency in tumour DNA causes shifts in the translational reading frame resulting in the production of altered peptides, or neopeptides that are recognised as foreign by the immune system, leading Dr. Westdorp and colleagues to investigate a preventive neoantigen-based vaccination using dendritic cells (DCs), which present antigen that results in T cell priming and activation. The investigators recruited 20 patients that were HLA-A*02.01 positive and carriers of germline MMR-gene mutation but did not have signs of Lynch syndrome-associated disease or were more than 5-years beyond detection of a non-metastasized Lynch syndrome-associated cancer. The primary endpoint was to investigate the safety and feasibility of DC vaccinations. Secondary objectives were to evaluate whether monocyte-derived peptide-loaded DC can induce an immune response to the selected neoantigens (caspase-5 and TGF-βRII) and the tumour-associated antigen carcinoembryonic antigen (CEA).

The investigators found that preventive DC vaccination was feasible and safe. Generally, DC vaccinations were well tolerated and no hospitalisations were required during study treatment. All vaccinated individuals experienced flu-like symptoms and 17 of 20 patients developed an injection site reaction following intradermal DC administration. One patient had grade 4 fever of more than 40^0 C for more than 24 hours, which lead to treatment discontinuation.

All immunised and tested patients demonstrated a cellular immune response against the control antigen. The investigators determined that 15 of the 20 immunised patients displayed functional neoantigen- or CEA-specific T cells in the challenged skin upon DC vaccination. NCT01885702. Westdorp *et al.* Abstract 1056PD

Practice point and future research opportunities

This study demonstrated that Lynch syndrome mutation positive carriers could be immunised with dendritic cells. The vaccination was feasible and safe and resulted in the majority of individuals having functional neoantigen- and CEA-specific immune responses. This study

opens the door for future investigation and immunotherapy trials of preventative immunisation with the intention of cancer prevention.

MELANOMA AND OTHER SKIN TUMOURS

Long-term results show adjuvant therapy with ipilimumab improves OS in high risk stage III melanoma

Alexander Eggermont, Institut Gustave Roussy, Villejuif, France presented long-term findings from the EORTC 18071 phase III trial evaluating ipilimumab as adjuvant therapy for patients with high-risk stage III melanoma. Beginning in 2008, the investigative team randomised 951 patients to ipilimumab at 10 mg/kg or placebo; 20%, 44%, and 36% of patients had stage IIIA, IIIB, or IIIC disease. The majority of patients (58%) had macroscopic lymph node involvement and the remaining patients had ulcerated primary melanoma. Results reported in 2015 showed that the trial met its primary endpoint of recurrence-free survival (RFS) after a median follow up of 2.3 years. Based upon these data, ipilimumab was approved by the US Food and Drug Administration (FDA) as adjuvant therapy for stage III melanoma.

At ESMO 2016, Professor Eggermont presented overall survival (OS) results from this trial after a median follow-up of 5.3 years that showed ipilimumab as adjuvant therapy significantly improved OS in these high-risk, stage III melanoma patients. Median OS was 86 months with ipilimumab versus not reached with placebo and the 5-year OS rates were 65.4% with ipilimumab compared to 54.4% with placebo, which represents a 28% reduction of the relative risk of death, hazard ratio [HR] 0.72 ($p = 0.001$). The 5-year RFS rates were 40.8% versus 30.3% with ipilimumab versus placebo, respectively, HR 0.76 ($p < 0.001$). The 5-year distant metastases-free survival rates were 48.3% with ipilimumab versus 38.9% with placebo, HR 0.76 ($p = 0.002$).

At the 5.3-year follow-up, immune-related grade 3-4 adverse events (AEs) included gastrointestinal events, reported in 16% of patients, hepatic in 11%, and endocrine AEs were reported in 8% of patients that resolved within 4 to 8 weeks, except the endocrine AEs, which took much longer to resolve or required permanent hormonal replacement therapies. Ipilimumab was discontinued due to an AE by 251 (53.3%) patients and 5 drug-related deaths occurred on study, as previously reported. These results were published simultaneously online in *The New England Journal of Medicine (NEJM)*. NCT00636168. Eggermont *et al.* Abstract LBA2_PR; *NEJM* 2016; 375:1845-1855.

Practice point and future research opportunities

Ipilimumab is an immune checkpoint inhibitor of cytotoxic T-lymphocyte antigen-4 (CTLA-4) that was approved in 2011 for first-line treatment of advanced melanoma in the US and Europe. This was the first trial to evaluate checkpoint blockade in the adjuvant setting in melanoma and the data reinforce ipilimumab as an important treatment option for these patients. The OS results reported at ESMO 2016 revealed clinically and statistically significant improvement with ipilimumab as adjuvant therapy in high-risk stage III melanoma patients.

These results also provide important scientific information: until now it was unknown whether ipilimumab, which works by stimulating the immune system against tumour antigens, or other immunotherapies could be effective in the adjuvant setting where there is microscopic residual disease that may or may not contain a sufficient amount of antigen to trigger a response. The risks and benefits of this option should now be discussed with patients; the toxicity is not negligible and patients need to be aware of the adverse event profile, and treatment should be reserved for experienced centres.

This trial represents an important milestone in the treatment of melanoma and the results open the door for other studies based on checkpoint blockade to try and improve cure rates in the adjuvant setting of melanoma, as well as other disease types. The results of several trials are anticipated, including EORTC 1325, which is investigating pembrolizumab, a PD-1 checkpoint blocking antibody, compared to placebo in the adjuvant setting.

Neoadjuvant ipilimumab plus nivolumab reduces pre-surgical tumour load in advanced melanoma

Christian Blank of the Netherlands Cancer Institute, Amsterdam, The Netherlands, and colleagues conducted the two-arm phase Ib OpACIN-neo trial in 18 patients with high-risk AJCC stage IIIB/C melanoma and palpable nodes. The patients' mean age was 54 years, WHO performance status was 0 for 8 patients in the adjuvant arm and for 10 patients in the neo-adjuvant arm, and the median number of lymph nodes involved was 2 (range: 1 to 4) and 1 (range: 1 to 5) in the respective arms. All patients received ipilimumab at 3 mg/kg plus nivolumab at 1 mg/kg; however, patients were randomised to receive either adjuvant 4 courses after surgery, or 2 courses each of split neo-adjuvant and adjuvant immunotherapy. The co-primary endpoints of the study were safety and feasibility, as measured by adverse events (AEs), adherence to timelines, and alteration in the magnitude or breadth of the neo antigen specific T cell response between pre- to post-adjuvant therapy. Secondary endpoints included relapse-free survival (RFS) by RESIST 1.1, and the rate and type of late adverse events.

Improved results were observed when combined ipilimumab and nivolumab were given pre- and post- surgery compared with only post-surgery administration. All 10 patients in the neo-adjuvant arm underwent lymph-node dissection at the pre-planned week 6 time-point. This regimen reduced the tumour burden by the scheduled surgery date without any delays in planned lymph node dissections. Tumour load was reduced after 6 weeks of ipilimumab plus nivolumab immunotherapy in 8 of 10 patients. Pathologic complete response (pCR) was achieved by 3 patients, and 5 patients showed minimal remaining micro-metastases, including one partial response (PR) with remaining metastasis of 0.5 mm. One patient showed stable disease and one patient experienced progressive disease (PD). The objective response rate (ORR) was 78%. So far, none of the responding patients within the neoadjuvant arm has relapsed.

No differences in surgery-associated AEs between adjuvant and neo-adjuvant immunotherapy were observed and no surgery-related AEs were attributed to the neoadjuvant immunotherapy. Only 2 of 18 patients received all 4 courses of immunotherapy; 15 patients halted treatment due to toxicity grades 2 to 4, and one patient due to PD following 2 courses of adjuvant

ipilimumab/nivolumab. All patients experienced an immunotherapy-related AE and 16 patients had a grade 3/4 AEs. The most commonly reported immunotherapy-related AES greater than grade 3 were diarrhoea in 4 patients, elevated lipase in 7, and colitis in 6 patients. Four patients reported elevated ALT, 3 patients each experienced rash and vomiting, headache, adrenal insufficiency, and fever each occurred in 2 patients and one case of hyperthyroidism was reported. At a median follow-up of 34 weeks, 7 of 8 patients had recovered from AEs and 12 patients have ongoing AEs; of these 8 require hormonal supplementation. The remaining 4 patients have low grade AEs of diarrhoea, elevated lipase, or hyperglycaemia. A phase II OpACIN-neo trial study is planned in collaboration with several melanoma institutes world-wide and will explore regimens that are adjusted to retain efficacy while reducing toxicity. NCT02437279. Blank *et al.* Abstract LBA39

Practice point and future research opportunities

The outcome of patients with high-risk stage III macroscopic/palpable melanoma is poor, with 5-year survival rates of just 20% to 59%. Adjuvant radiotherapy after lymph node dissection improves the local control but has no effect on RFS or OS. Immunotherapy initiated prior to surgery successfully reduced tumour burden and allowed on-schedule lymph node dissection in all patients with high-risk stage III melanoma in the neo-adjuvant arm. Neo-adjuvant ipilimumab plus nivolumab is feasible, results in on-time surgery, and induces a high frequency and depth of responses.

First-line dabrafenib/trametinib combination in melanoma supported by long-term results

Lead author Caroline Robert, Institut Gustave Roussy, Paris, France discussed the co-inhibition of BRAF and MEK pathways with dabrafenib and trametinib, which continued at 3 years to be superior to sole BRAF inhibition with vemurafenib in patients with unresectable metastatic melanoma. Dr. Robert presented an updated survival analysis from the phase III COMBI-v trial, which randomised 704 patients with advanced, treatment-naive, BRAF-mutated, stage III/IV melanoma 1:1 to dabrafenib at 150 mg twice daily plus trametinib at 2 mg daily or to the standard dose of vemurafenib at 960 mg twice daily. A total of 33 (9%) patients in the vemurafenib arm crossed over to the combination arm after the interim analysis. The primary endpoint of COMBI-v was overall survival (OS), while secondary endpoints were progression-free survival (PFS), overall response rate (ORR), duration of response (DOR), and safety.

The updated analysis occurred following 411 deaths and 16 months of additional follow-up since the 2-year data cut-off, which was July 2016. Patients receiving the combination had a 3-year OS rate of 45% (95% confidence interval [CI] 39.1, 49.8) compared with 32% (95% CI 26.1, 36.4) for vemurafenib monotherapy, hazard ratio 0.68. The 3-year PFS rates were 25% with dabrafenib plus trametinib and 11% with vemurafenib. The median duration of exposure was 12.2 months (95% CI 0.1, 47.3) with the combination versus 6.7 months (95% CI 0.1, 42.4) with vemurafenib.

Response was higher in the combination arm where the ORR was 67% versus 53% with monotherapy. Complete responses (CRs) were achieved by 68 (19%) versus 41 (12%) patients, partial responses (PR) by 48% versus 41%, and stable disease was observed in 24% versus 31% of patients receiving the combination versus vemurafenib, respectively. Progressive disease was reported for 6% and 11% of patients in the respective arms, and 8% of patients overall were not evaluable for response. The median DOR was 13.8 months with the combination versus 7.6 months with single-agent vemurafenib.

Subgroup analysis identified patients with baseline levels of lactate dehydrogenase (LDH) equal to or less than the upper limit of normal (ULN) who performed particularly well with combined therapy; 56% of these patients achieved 3-year OS with the combination versus 39% of patients on the vemurafenib arm. Median OS was not reached with combination treatment versus 21.6 months with vemurafenib. Three-year PFS rates in this subset were 33% versus 13%; median PFS was 17.5 versus 9.2 months (HR, 0.56) with the combination versus monotherapy, respectively.

In contrast, in the cohort of patients with LDH > ULN, 20% of patients achieved 3-year OS versus 14% of patients on vemurafenib, median OS was 10.8 versus 8.7 months with monotherapy (HR, 0.79). Median PFS in this subset at 3 years was 5.5 months versus 4 months (HR, 0.70) with dabrafenib/trametinib and vemurafenib, respectively. When the subset of patients with normal LDH was combined with patients having fewer than 3 sites of metastases, 3-year OS rates rose to 70% versus 46%, and PFS rates were 39% with the combination versus 15% with single-agent vemurafenib.

Dabrafenib/trametinib was found to have a manageable adverse event (AE) profile, with no new safety signals reported. Sixteen percent of patients discontinued treatment due to AEs with dabrafenib/trametinib versus 15% who received vemurafenib. The most commonly reported grade 3/4 AEs in the combination arm included hypertension (15%) and pyrexia (5%). NCT01597908. Robert *et al.* Abstract LBA40

Practice point and future research opportunities

These findings support the long-term use of dabrafenib plus trametinib as a standard first-line treatment for patients with BRAF, V600 negative–mutant metastatic melanoma. Improved outcomes with the combination over vemurafenib were demonstrated despite crossover. COMBI-v is the second trial to show superiority for the combination versus monotherapy in advanced melanoma; the phase III COMBI-d trial showed 3-year OS rates of 44% versus 32% with the combination versus dabrafenib alone, respectively. Patients with low LDH responded extremely well to the targeted treatment, which was especially effective in patients with low LDH and fewer that 3 metastatic sites.

Final OS data for KEYNOTE-002 with pembrolizumab in ipilimumab-refractory melanoma

Omid Hamid of the Melanoma & Skin Cancers Centre, The Angeles Clinic and Research

Institute, Los Angeles, USA, presented final overall survival (OS) results on behalf of the KEYNOTE-002 investigators. Previously reported findings from KEYNOTE-002 demonstrated the superiority of pembrolizumab over investigator-choice chemotherapy in patients with advanced melanoma and confirmed progression after 2 or more doses of ipilimumab, hazard ratio [HR] 0.57 ($p < 0.0001$) for pembrolizumab at 2 mg/kg Q3W and HR 0.50 ($p < 0.0001$) for pembrolizumab at 10 mg/kg Q3W.

KEYNOTE-002 randomised 180 patients to pembrolizumab 2 mg/kg every 3 weeks, 181 patients to pembrolizumab at 10 mg/kg every 3 weeks, and 179 to investigator's choice of chemotherapeutic agents, including dacarbazine, temozolomide, carboplatin, paclitaxel, or the latter two in combination. Crossover to pembrolizumab was allowed upon progression in the chemotherapy arm.

As of November 16, 2015, median follow-up was 13.5 months and 368 deaths had occurred. The study found that both doses of pembrolizumab produced superior OS compared with chemotherapy. Median OS was 13.4 and 14.7 months at the respective pembrolizumab doses versus 11.0 months with chemotherapy. The OS rates at 18 months were 40% and 44% versus 36%, and 24-month OS rates were 36%, 38%, versus 30%, respectively with pembrolizumab at 2 mg/kg and 10mg/kg versus chemotherapy. The HR for OS was 0.86; 95% confidence interval [CI] 0.67, 1.10 for 2 mg/kg ($p = 0.1173$) and HR 0.74; 95% CI 0.57, 0.96 for 10 mg/kg ($p = 0.0106$), with no difference observed between doses, HR 0.87.

Crossover patients also demonstrated improved OS with pembrolizumab. Upon experiencing progression in the chemotherapy arm, 98 (55%) patients crossed over and were censored; the HR was 0.79; 95% CI 0.58,1.08 for 2 mg/kg ($p = .0683$) and HR 0.67; 0.49, 0.92 for 10 mg/kg ($p = 0.0068$), also showing no difference between doses, HR 0.87. In this cohort, the 24-month PFS rates were 16% for 2 mg/kg, 22% for 10 mg/kg versus <1% with chemotherapy. The objective response rates were 22%, and 28%, versus 4%; no disease progression at the time of the analysis was observed in 73%, 74%, and 13% of responders, respectively, in the 2 mg/kg and 10 mg/kg pembrolizumab versus chemotherapy cohorts.

In addition, grade 3 to 4 toxicities were less frequent with both doses of pembrolizumab at 13% and 17% versus 26% with chemotherapy, even though pembrolizumab exposure was more than triple at mean 232 days and 276 days versus 82 days with chemotherapy. NCT01704287, Hamid *et al.* Abstract 1107O

Practice point and future research opportunities

The KEYNOTE-002 study long term follow-up findings demonstrate that pembrolizumab prolonged OS over chemotherapy in population of patients with ipilimumab-refractory melnoma, although with a 55% crossover rate, the difference did not reach statistical significance for either dose of pembrolizumab. Taken together with the significant PFS benefit, durable responses, and

favourable safety profiles, these data support pembrolizumab in patients with ipilimumab-refractory melanoma.

Safety and efficacy of anti-PD-1 antibodies in elderly patients with metastatic melanoma

Rajat Rai of the Melanoma Institute Australia, University of Sydney in North Sydney, Australia noted that, even though melanoma incidence increases with age and anti-PD-1 antibodies are often the first option for elderly patients with metastatic melanoma, limited data exist on the safety and efficacy of anti-PD-1 antibodies in this age group. With colleagues, Dr. Rai reviewed data from all patients treated with PD-1/PD-L1 antibodies in clinical trials at 4 centres, including patient demographics, primary and metastatic melanoma characteristics, toxicity, response, and survival data. Efficacy and safety following anti-PD-1/L1 treatment was compared in patients aged >75 years with patients ≤75 years. The analysis comprised 283 patients with a median follow-up of 44.5 months. Pembrolizumab had been given to 208 patients and 71 received nivolumab.

The majority, (75%) of patients had American Joint Committee on Cancer (AJCC) stage M1c disease, 57% were ECOG performance status 0, 40% of patients had elevated LDH, 14% of patients received treatment for stable brain metastases. Prior treatment with ipilimumab had been received by 124 (43%) patients, and 63 (22%) received MAPK inhibitors. These prognostic factors were similar in the cohort of 35 (12%) patients older than 75 years old, and in the cohort of 159 (47%) patients aged ≤75years; overall, the patients in both arms had received similar rates of prior ipilimumab, but fewer patients in the older group had received MAPK inhibitors compared with younger patients (p = 0.04).

The objective response rates (ORRs) were similar in both arms; in patients >75 the ORR was 48% compared to 34% in patients ≤75 years. There was no difference in the incidence of immune-related adverse events in elderly versus younger patients (p > 0.05), and the rates of discontinuation for toxicity were equivalent at 0.05% in both groups (p > 0.05). Median progression-free survival (PFS) and overall survival (OS) were 8.7 months and 33.5 months, respectively in older patients compared to PFS of 4.6 months and OS of 48.1 months in younger patients (p = 0.48). Rai 3001 *et al.* Abstract 1113PD

Practice point and future research opportunities

In this retrospective analysis, immunotherapy with anti-PD-1/L1 antibodies in elderly patients aged 75 and older with metastatic melanoma was safe and effective. These results support the consideration of immunotherapy in elderly patients who demonstrated similar responses and toxicity profiles as those of patients with metastatic melanoma younger than 75 years.

Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases

Lead author John J. Park, Medical Oncology, Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, Australia presented findings from a retrospective analysis of the efficacy of anti-PD-1 agents in patients with metastatic melanoma and brain metastases who were treated in 4 centres. The analysis included patient demographics, tumour characteristics, and treatment history including intracranial and extracranial response rates and progression-free survival (PFS). Response was determined by modified RECIST where up to 5 intracranial (IC) target lesions were used for intracranial assessment.

This interim analysis was done at a median follow-up of 8.5 months and included data from 39 patients; 77% of patients were male and 9 (23%) patients were to receive anti-PD-1 as first-line therapy. At the start of PD-1 inhibitor treatment, 56% patients had an elevated LDH. ECOG performance status of 0-1, 2 and >2 was reported in 64%, 26% and 10% of patients, respectively. The patients had a median of 4 intracranial lesions (range: 1 to 20) and 26 (67%) patients had received local therapy of radiotherapy or surgery for brain metastasis. BRAF mutation was detected in 23 (59%) patients, Dexamethasone at doses ranging from 0.5 to 8 mg was administered to 13 (33%) patients.

Following anti-PD-1 treatment the best intracranial response rate was 26%, which included 18 patients with symptomatic brain metastases and 13 patients receiving steroids. Of these 10 patients, 2 had not received prior radiotherapy, 3 were receiving concurrent radiotherapy, and 5 patients had received prior radiotherapy. Stable disease was achieved by 8 patients and 12 patients experienced progressive disease. The median intracranial PFS was 2.1 months (95% confidence interval [CI] 1.3, 2.9). The extracranial response rate was 17% and median PFS was 2.1 months (95% CI 1.9, 3.4). Analysis of the full patient cohort is ongoing. Park *et al.* Abstract 1114PD

Practice point and future research opportunities

This study provides data regarding the use of anti-PD-1 immunotherapy in patients with metastatic melanoma and untreated, symptomatic, or progressing brain metastasis, a patient population with a poor prognosis and limited data on the efficacy and safety of these agents in this cohort exist. Intracranial responses to anti-PD-1 agents were seen in patients with symptomatic brain metastases and in patients on corticosteroids. Data from the prospective trials evaluating anti-PD-1 therapy in patients with brain metastasis that are underway will also contribute to the understanding of the efficacy and safety of anti-PD-1 therapy in these patients.

PALLIATIVE AND SUPPORTIVE CARE

Evaluation of the effect of early palliative care versus standard of care on QoL of advanced cancer patients

Vittorio Franciosi, Medical Oncology Unit, University Hospital in Parma, Italy and colleagues assessed the impact of early palliative care (EPC) on the quality of life (QoL) in patients with advanced cancer in 4 ESMO Designated Centres of Integrated Oncology & Palliative Care (ESMO-DC). In this randomised study, 139 patients were assigned to Standard Oncologic Care (SOC) alone and 142 patients to SOC integrated with EPC. All patients had been diagnosed within the previous 8 weeks with advanced cancer, including non-small cell lung cancer (NSCLC), gastric, pancreatic, and biliary cancers. No significant differences were observed between the 2 cohorts in terms of patient demographics such as the type of first line chemotherapy; age, sex, disease stage or type of cancer, and ECOG performance status. Each arm was extremely well-balanced. QoL was assessed at baseline and at 12 weeks using the Functional Assessment of Cancer Therapy - General (FACT-G) scale. Primary endpoint was the change in the QoL scores at week 12 from baseline.

The FACT-G baseline questionnaires were evaluable in 103 (74%) patients in the SOC control arm and 111 (78%) patients in the EPC arm who demonstrated mean (standard deviation) FACT-G baseline scores of 67.9 (15.4) versus 68.5 (15.3) in the respective arms (T-test p = 0.77). This study did not demonstrate that EPC improved QoL in patients with advanced disease. At 12 weeks, the mean (standard deviation) difference in scores for FACT-G scores was 3.5 points (14.5) for SOC control patients and 4.1 points (13.9) in the EPC arm and was not statistically significant (T-test p = 0.75). The authors advised that future studies should be focused on single tumours, using instruments for measuring QoL-specific cancer and they are participating in analyses in progress to study the phenomenological complexity and identify clusters of patients in whom the EPC could be effective. Project code E35E13000030002. Franciosi *et al.* Abstract LBA49

Practice point and future research opportunities

Although this trial did not show a statistically significant difference in quality of life between cohorts of patients receiving standard of care and those offered EPC at 12 weeks, measured with FACT-G, the value of EPC due to different profile of ESMO-DC and the heterogeneity of the tumour sites, could have reduced the effect of the EPC in this study.

Paradigm shift needed in end of life use of chemotherapy

Phillipe Rochigneux, Medical Oncology, Institute Paoli-Calmettes, Marseille, France called for a paradigm shift in end of life care from administering chemotherapy to initiating palliative care at an earlier stage and formulating clear guidelines for end of live care. Chemotherapy is often administered near the end of life for patients with solid cancers with the intent to ease symptoms but is usually ineffective and toxic. Dr. Rochigneux presented findings on behalf of colleagues

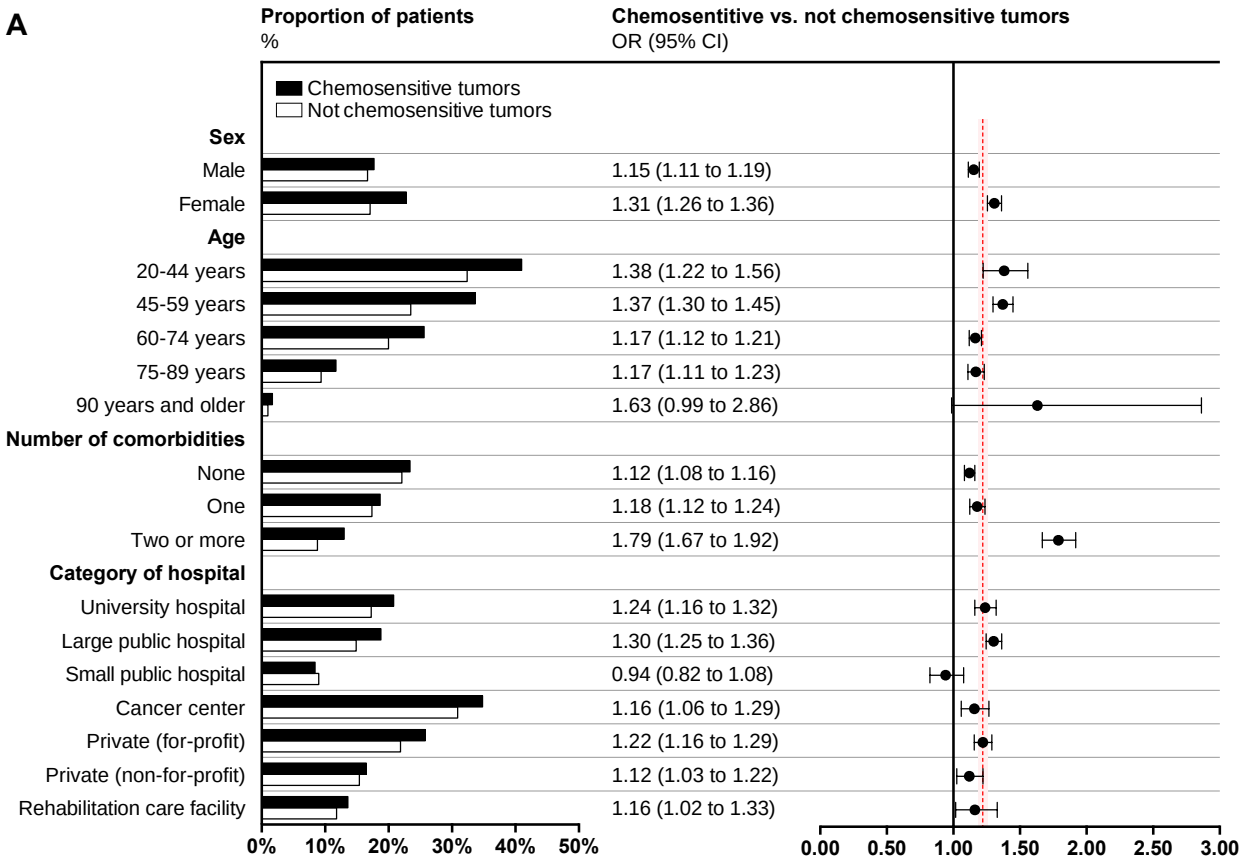
from a large audit of data concerning the use of chemotherapy at the end of life throughout France and the factors associated with its use. The investigators designed a nationwide, register-based study that included all patients with metastatic solid tumours who were hospitalised between 2010 and 2013 who were aged 20 years and older, and who died. They used multivariate analyses to identify patients, tumour, and the facility level characteristics associated with chemotherapy use. Specific sub-analyses were also computed to investigate the role of the putative chemosensitivity of the tumour, as defined by a response rate of the tumour to standard first line chemotherapy > 30% (literature data).

Data regarding 279,846 metastatic solid cancers in end of life patients were included in the register, which revealed that chemotherapy was administered near the end of life at rates of 39.1% during the last 3 months, 19.5% during the last month, and 11.3% within the final 2 weeks. During their last month of life, 6.6% of patients started or resumed a chemotherapy regimen.

Patient characteristics that independently associated by multivariate analysis with lower rates of chemotherapy included female sex (odds ratio [OR] 0.96; 95% confidence interval [CI] 0.93, 0.98), older age (OR 0.70; 95% CI 0.69, 0.71 for each 10-year increase), and a higher number of chronic comorbidities (OR 0.83; 95% CI 0.82, 0.84).

Patients were more likely to receive chemotherapy during the last month of life if their tumours displayed chemosensitivity to standard first line chemotherapy (OR 1.21; 95% CI 1.18, 1.25). Another factor that independently associated with end of life chemotherapy were patients having cancer types for which major therapeutic innovations occurred between the years 2005 to 2010 (OR 1.17; 95% CI 1.14,1.20).

End-stage chemotherapy rates were also higher in patients dying in a for-profit hospital compared with university hospitals (OR 1.40; 95% CI 1.34,1.45), and in patients in comprehensive cancer centres (OR 1.43; 95% CI 1.36,1.50). Higher than average rates of chemotherapy were reportedly administered near the end of life in high-volume cancer centres and in hospitals lacking palliative care units (OR 1.21; 95% CI 1.18, 1.24). Rochigneux *et al.* Abstract 1300O



Association between the chemosensitivity of different solid tumours and the likelihood of receiving chemotherapy in the last month before death (n=182,938).

© Phillipe Rochigneux.

Practice point and future research opportunities

This large analysis demonstrates that chemotherapy rates near the end of life remain high in patients with metastatic solid cancers, and are especially high for younger patients, being treated in high-volume centres, which lack a palliative care unit. There is an urgent need to decrease the aggressiveness of end of life treatments by making and implementing clear guidelines for end of life care, to initiate palliative care earlier on, and to reinforce supportive care training for oncologists and other cancer professionals.

Proposed pegfilgrastim biosimilar MYL-1401H demonstrated equivalence to EU-neulasta® in the prophylaxis of chemotherapy-induced neutropenia

Cornelius F. Waller, Department of Haematology, Oncology and Stem Cell Transplantation, University Medical Centre Freiburg and Faculty of Medicine, University of Freiburg, Freiburg, Germany and colleagues conducted this phase III trial to evaluate whether the pegfilgrastim

biosimilar, MYL-1401H has equivalent efficacy and safety as EU-Neulasta® when used as prophylaxis for chemotherapy induced neutropenia in patients with stage II/III breast cancer. The investigators conducted this, multicentre, randomised, double-blind, parallel-group trial in patients that were chemotherapy and radiotherapy naive and had been newly diagnosed with stage II/III breast cancer. Patients were treated with docetaxel, doxorubicin, and cyclophosphamide chemotherapy every 3 weeks for 6 chemotherapy cycles. The per protocol population of 194 patients was randomised in a 2:1 ratio to also receive 6 mg/0.6 mL of either MYL-1401H or EU-Neulasta® on day 2 of each chemotherapy cycle.

The primary efficacy endpoint was the duration of severe neutropenia (DSN) experienced by patients during cycle 1, defined as days with absolute neutrophil count (ANC) < 0.5 × 109/L in the per protocol population. Equivalence could be declared if the two-sided 95% confidence interval (CI) of the least squares means difference between the DSNs falls wholly within an equivalence region defined as [-1, +1 day]. A sensitivity analysis in the intent-to-treat population was also carried out.

The mean (standard deviation) DSN in the MYL-1401H and EU-Neulasta® groups was 1.2 (± 0.93) and 1.2 (± 1.10), respectively. The 95% CI of least squares means difference of -0.285 day, 0.298 day was within predefined range, and was also corroborated by the sensitivity analysis. All other endpoints of the study, including grade 3/4 neutropenia, time to ANC nadir, and duration of post-nadir recovery were also comparable. The overall safety profile of MYL-1401H was similar to EU Neulasta® with patients in both arms most frequently reporting bone pain, an expected treatment emergent adverse event. EudraCT Number: 2014-002324-27. Waller *et al.* Abstract 1433O

Practice point and future research opportunities

The proposed biosimilar, MYL-1401H, demonstrated equivalent efficacy to EU-Neulasta® in the prophylaxis of chemotherapy induced neutropenia in patients with newly diagnosed breast cancer. MYL-1401H was generally well tolerated and there were no particular safety concerns identified, with overall safety profile being similar to EU-Neulasta®. These data support the licensing of MYL-1401H, which could result in lower treatment cost in offering prophylaxis for chemotherapy-induced adverse events, such as neutropenia.

Exploration of the heterogeneity of moderately emetogenic chemotherapy on response to fosaprepitant in a randomised phase III trial

Lead author Cindy Weinstein, Department of Clinical Research, Merck & Company, Kenilworth, USA presented findings from a phase III, global, randomised, double-blind, parallel-group study evaluating the efficacy of fosaprepitant as emetic prophylaxis in adult patients scheduled to receive an intravenous dose of ≥1 moderately emetic chemotherapy (MEC) agents on treatment day 1. This large study randomised 1000 patients to a control regimen consisting of 8 mg oral ondansetron, 20 mg dexamethasone, and i.v saline as placebo prior to the first MEC dose on

day 1 followed by 8 mg oral ondansetron 8 hours after the first dose, and every 12 hours on days 2 and 3 or to a fosaprepitant regimen, which consisted of the same dose of oral ondansetron on day 1, along with 12 mg dexamethasone and a single dose of fosaprepitant at 150 mg i.v. before the first dose of MEC on day 1, with no additional prophylactic antiemetic beyond day 1.

The trial met the primary endpoint of complete response, defined as no vomiting or rescue medication in the delayed phase from 0 to 120 hours following MEC. The intent-to-treat treat population comprised 502 patients in the fosaprepitant arm and 498 control patients. Fosaprepitant patients achieved complete response versus control ($p < 0.001$). Single-day MEC regimens were used by 71.3% of patients in the fosaprepitant group and 69.9% of patients in the control group; of these, 51.2% and 51.4% received carboplatin-based chemotherapy in the fosaprepitant and control groups, respectively. Complete response in the delayed phase was achieved by 77.9% of patients on fosaprepitant receiving single-day chemotherapy and by 80.3% receiving multiple-day chemotherapy versus 64.7% and 77.1% of control patients receiving single and multiple MEC, respectively. In the fosaprepitant arm, no difference was observed between the rates of complete response in the delayed phase in patients receiving carboplatin (78.2%) versus non-carboplatin (79.6%). In the control group, a difference in complete response was seen during the delayed phase where complete response was achieved by 64.1% of patients on carboplatin compared to 73.1% of patients receiving a non-carboplatin MEC. NCT01594749. Weinstein *et al.* Abstract 1435O

Practice point and future research opportunities

A single-day triple-antiemetic fosaprepitant regimen has demonstrated superiority to a standard 3-day regimen for preventing chemotherapy induced nausea and vomiting in subjects receiving non-anthracycline and cyclophosphamide-based MEC. This study demonstrates the efficacy of a single-day fosaprepitant regimen in preventing nausea and vomiting in subjects receiving non-anthracycline and cyclophosphamide-based MEC with/without carboplatin and in both single- and multiple-day chemotherapy regimens. Fosaprepitant has the additional advantage of requiring a single administration to control symptoms during the delayed phase.

SARCOMA

Neoadjuvant chemotherapy in patients with localised high-risk STS

No additional benefit was observed from chemotherapy regimens that were matched to specific histologic subtypes of sarcoma but the study did show that neoadjuvant chemotherapy with an anthracycline plus ifosfamide associates with significant survival gains in patients with localised high grade soft tissue sarcoma (STS) of the trunk or extremities. Alessandro Gronchi, Chair of the Sarcoma Surgery at the National Cancer Institute, Milan, Italy presented findings from an interim analysis on behalf of the Italian Sarcoma Group from a multi-centre study, of patients with localised high-risk STS of the trunk or extremities. The study compared neoadjuvant chemotherapy with chemotherapy regimens that were tailored to the individual histology sub-types based upon previously published data. Patients with one of the 5 sarcoma histological subtypes were randomised 1:1 to receive pre-operative treatment with either 3 cycles of epirubicin at 120 mg/m^2 plus ifosfamide at 9 g/m^2, or to receive 3 cycles of one of the following histology-based regimens:

- Trabectedin in 65 patients with high-grade myxoid liposarcoma
- Gemcitabine/docetaxel in 97 undifferentiated pleomorphic sarcoma patients
- High-dose prolonged-infusion ifosfamide in 70 patients with synovial sarcoma
- Gemcitabine/dacarbazine in 28 patients with leiomyosarcoma
- Etoposide/ifosfamide in 27 patients with malignant peripheral nerve sheath tumours

After a median follow-up of 12.3 months, patients randomised to epirubicin plus ifosfamide showed significantly higher probability of relapse-free survival (RFS) at 46 months regardless of underlying histological subtype compared to patients randomised to a histology-driven regiment; the RFS probability was 0.62 versus 0.38 ($p = 0.004$), and the probability of overall survival (OS) was 0.89 versus 0.64, ($p = 0.033$). The study was halted early.

Subgroup analysis showed that patients with high-grade myxoid liposarcoma fared as well on trabectedin as with neoadjuvant chemotherapy; this subgroup demonstrated similar progression-free survival and OS to patients receiving epirubicin plus ifosfamide. This was an important finding, since trabectedin is far less toxic than conventional chemotherapy, according to the authors who now plan to expand this subgroup to evaluate whether there is a difference between the treatments in terms of outcomes. NCT01710176; EUDRACT 2010 – 023484 – 17. Gronchi *et al.* Abstract LBA6_PR

Practice point and future research opportunities

The benefit of adjuvant chemotherapy in STS has been controversial in recent years due to contradictory study outcomes. From this study, it may be concluded that neoadjuvant anthracycline plus ifosfamide is better than the histology-driven regimens, but it remains unresolved whether neoadjuvant chemotherapy is better in comparison to no treatment. To address this controversy, it is necessary to show that using a neo-adjuvant therapy in patients affected by localised high risk STS of the extremities or trunk wall is associated with a clear-cut OS and RFS advantage, as compared with any other strategy, including no treatment.

No additional benefit with evofosfamide in combination with doxorubicin over doxorubicin monotherapy in patients with advanced STS

The results for evofosfamide, a prodrug that is activated under hypoxic conditions commonly found in the tumour microenvironment and leads to DNA alkylation, were reported by lead author William Tap, Oncology, Memorial Sloan-Kettering Cancer Center, New York, USA. Evofosfamide was tested in multi-national, open-label, phase III trial that randomised equally 640 patients to doxorubicin on day one or doxorubicin plus evofosfamide at 300 mg/m^2 i.v. on days 1 and 8 of a 21-day cycle. The patients had locally advanced unresectable or metastatic soft tissue sarcoma (STS), intermediate or high grade, ECOG performance status 0/1, and measurable disease by RECIST 1.1. Leiomyosarcoma was confirmed in 36% of patients, 17% had liposarcoma, and 12% of patients had undifferentiated pleomorphic sarcoma. Metastatic disease was reported for 89% of patients and 11% had locally advanced disease. The primary endpoint was overall survival (OS).

A median of 6 cycles were delivered and the docetaxel dose intensity was >90% through 6 cycles, in both arms. The 317 patients in the evofosfamide/docetaxel showed poorer outcomes than the 323 patients on docetaxel and the primary endpoint of OS was not met, (hazard ratio [HR] 1.06; 95% confidence interval [CI] 0.88, 1.29). The median OS was 18.4 months with the combination versus 19.0 months with docetaxel. Although the response rate favoured the combination, no statistically significant difference was observed in progression-free survival (PFS) between the groups. The response rate was 28.4% with evofosfamide/docetaxel versus 18.3% with docetaxel, odds ratio 1.77; 95% CI 1.20, 2.58 (p = 0.003). Median PFS was 6.3 months on evofosfamide/docetaxel versus 6.0 months on docetaxel, HR 0.85; 95% CI 0.70, 1.03 (p = 0.099).

The most common grade 3/4/5 adverse events (AEs) were anaemia (35%), neutropenia (33%) and leucopenia (18%). Febrile neutropenia occurred in 18% of patients on evofosfamide/docetaxel and 11% of patients on docetaxel. The AEs leading to death were reported in 2.6% of patients on evofosfamide plus docetaxel and for 1.0% of patients on docetaxel. The AEs led to discontinuation in 8.3% and 6.2% of patients in the respective treatment arms. NCT01440088. Tap *et al.* Abstract 1395O

Practice point and future research opportunities

The combination of evofosfamide/docetaxel did not improve OS or PFS compared to docetaxel alone. The safety profile was consistent with previous reports. Evofosfamide is still being evaluated in pancreatic cancer and soft tissue sarcoma.

PFS improved with trabectedin over BSC in patients with pretreated advanced STS

Axel Le Cesne, Department of Medicine, Institut Gustave Roussy, Villejuif, France and colleagues in the French Sarcoma Group assessed the efficacy, safety and quality of life of trabectedin versus best supportive care (BSC) as a second or later treatment line in patients with advanced soft tissue sarcoma (STS) in the phase III, multicentre T-SAR trial. The trial enrolled 103 patients with histologically proven advanced STS, including both lipo-leiomyosarcoma and non lipo-leiomyosarcoma histotypes, who progressed after at least one anthracycline-containing regimen but had received fewer than 3 previous chemotherapy lines.

The patients had ≥1 measurable baseline lesion (RECIST v.1.1) and were stratified according to lipo-leiomyosarcoma status; 60.2% of patients had lipo-leiomyosarcoma and 39.8% of patients had non lipo-leiomyosarcoma The patients had WHO performance status scores of 0 or 1, and were required to have adequate haematological and hepatic function. The investigators randomised 52 patients to trabectedin at 1.5 mg/m^2 intravenously for 24 hours for 21 days and 51 patients to best supportive care (BSC) until progressive disease (PD), unacceptable toxicity, or patient's request. Crossover to trabectedin upon PD was allowed for patients receiving BSC. The primary endpoint was progression-free survival (PFS), which was defined as time from randomisation to PD or all-cause death.

After 88 cases of PD were observed the data were evaluated for PFS. The patients receiving trabectedin demonstrated significantly prolonged PFS compared to patients receiving BSC; the median PFS was 3.12 months with trabectedin compared with 1.51 months with BSC, hazard ratio [HR] 0.39; 95% confidence interval [CI] 0.26, 0.63 ($p < 0.0001$). The response to trabectedin was strongest in patients with lipo-leiomyosarcoma where the median PFS was 5.13 months with trabectedin versus 1.4 months with BSC, HR 0.29; 95% CI 0.15, 0.55 ($p < 0.0001$). In the non lipo-leiomyosarcoma cohort the median PFS was 1.81 versus 1.51 months with trabectedin versus BSC, respectively, HR 0.60; 95% CI 0.29, 1.26 ($p = 0.18$). 2014-003176-23. Le Cesne *et al.* Abstract 1396O

Practice point and future research opportunities

Although trabectedin has demonstrated single-agent activity in patients with pretreated advanced STS and has been approved in Europe since 2007 for this indication, trabectedin had not been compared with BSC in a randomised trial comprising patients with all sarcoma histotypes. The pre-planned analysis in this study demonstrated a significant improvement in median PFS with trabectedin over BSC in patients with pretreated advanced STS of multiple histologies, thereby meeting the primary endpoint of the study. Trabectedin had a major impact in the lipo-leiomyosarcoma STS cohort whereas in the non lipo-leiomyosarcoma STS group the

median PFS was lower and similar to that seen in the BSC cohort and showed a statistically non-significant difference, suggesting that these patients could benefit more from a treatment other than trabectedin.

The NETSARC reference network of sarcoma patients shows a major impact of multidisciplinary board presentation prior to first treatment

Jean-Yves Blay, Medical Oncology, Centre Léon Bérard, in Lyon, France, presented outcomes of the 26,883 patients registered in the NETSARC multidisciplinary tumour boards (NMTB) and demonstrated how NMTB discussion enabled better care for these patients. This network of 26 reference centres for sarcoma in France was designated by the French National Cancer Institute in 2009 and includes the patient characteristics, treatment and diagnosis procedures, disease progression, and survival information for patients with sarcomas.

Soft tissue, visceral, and bone sarcomas represent 17,801 (66%), 4,625 (17%), and 4,457 (17%) patients, respectively. Individual NETSARC centres managed a median of 404 (range: 92.2 to 974) patients in 5 years.

The median follow-up of the series in this study was 26 months (range: 6 to 590 months). During this time, 13,845 women (52%) and 13,038 men (48%), with a median age of 60 years (range: 0 to 101) were treated within the NETSARC network. The most frequently diagnosed histotypes were leiomyosarcoma, gastrointestinal stromal tumour (GIST), liposarcoma, and undifferentiated pleomorphic sarcoma. At diagnosis, 11% of patients presented with metastases and 37% of patients were presented to a NMTB prior to initial treatment. At 24 months, local and metastatic relapse rates were 24% and 22%, respectively. The 24-month overall survival rate was 87%.

Investigators reviewed relapse rates in patients not reviewed and those reviewed by NMTB prior to treatment and found the local relapse rate (LRR) was significantly lower in patients discussed in NMTB prior to receiving the first treatment; LRR was 22% for non-reviewed versus 29% for reviewed patients at 24 months ($p = 0.000$); however, metastatic relapse rates did not significantly differ between these groups. Patients discussed in NMTB prior to the first treatment had significantly larger tumours of a higher grade that were more frequently deep-seated and located in the head/neck or internal trunk ($p = 0.000$ all comparisons).

In multivariate analysis, the lack of discussion in NMTB prior to initial treatment emerged as an independent unfavourable prognostic factor for relapse, (hazard ratio [HR] 1.9; 95% confidence interval [CI] 1.6, 2.2) together with age, grade, tumour size, depth and tumour location (all p values < 0.001), and lack of discussion was also associated with the highest hazard ratio along with tumour status of grade 3. Blay *et al.* Abstract 1397O

Practice point and future research opportunities

This large audit demonstrates how discussion of patients by multidisciplinary tumour boards prior to the first treatment resulted in overall better outcome for these patients that associated with a

lower rate of relapse. The relapse rate was found to be higher in this large real-life series of 26,883 sarcoma patients of the NETSARC network than that previously published in the literature.

Characterisation of the tumour microenvironment reveals CD8 T-cell presence associates with improved outcome in localised osteosarcoma

Emanuela Palmerini, Muscoloskeletal Oncology, Istituto Ortopedico Rizzoli in Bologna, Italy and colleagues investigated whether immune infiltrates were associated with superior survival, and examined primary osteosarcoma tissue microarrays (TMA) to test this hypothesis. The investigators analysed biopsies from 129 patients that were prospectively treated from April, 2001 to November, 2006 and TMA from representative areas were assembled. Clinical and pathological characteristics at diagnosis, immunological characterisation including immune cell markers (CD8, CD4, CD3, FOXP3, CD20, CD68) of the tumour microenvironment (TME), PD-1 expression on TME, and PD-L1 both on tumour cells and in the TME were correlated with outcome.

Of the 129 enrolled patients, samples from 86 patients had adequate staining for all markers. The 86 patients had a median age of 16 (range: 4 to 39) years; high LDH was reported in 36 patients and high alkaline phosphatase (AP) in 18 patients. All patients underwent neoadjuvant chemotherapy and surgery, which resulted in a good pathologic response of ≥90% necrosis in 45 patients. The immunohistochemistry revealed that no patients had a tumour that expressed PD-L1but 12 patients had a TME that was positive for PD-L1. PD-1 expression was identified in the tumour and TME of 67 and 74 patients, respectively. CD8, CD3, FOXP3, CD20, and CD68 were detected in the TME of 74, 77, 28, 25, and 85 patients, respectively.

At a median follow-up of 8 years (range: 1 to 13 years), the 5-year overall survival (OS) was 74% (95% confidence interval [CI] 64, 85). Univariate analysis showed better 5-year OS associated with good responders (good 89% versus poor 57%, p = 0.0001), patients with CD8 tumoural infiltrates (CD8+ 78% versus CD8- 50%, p = 0.003), and with patients with normal AP (AP normal 85% versus AP high 44%, p = 0.04). A non-significant inferior 5-year OS was found in PD-L1 (TME) positive cases (PD-L1-positive 58% versus PD-L1 negative 77%, p = 0.14). No statistically significant difference in 5-year OS according to PD-1, FOXP3, CD68, CD20, age, gender or LDH status was observed. By multivariate analysis, good histologic response (p = 0.002) and CD8 infiltration (p = 0.02) were independently correlated with better survival. Palmerini *et al.* Abstract 1399PD

Practice point and future research opportunities

This study confirms the importance of good pathologic response, but also supports the hypothesis that CD8+ T effector cells present in the tumour microenvironment at diagnosis associates with superior survival for patients with localised osteosarcoma and further evaluation as a prognostic factor is warranted.

THORACIC MALIGNANCIES - NSCLC, Early Stage

Tumour downsizing possible with neoadjuvant immunotherapy given prior to surgery in early NSCLC

Findings from the first study of neoadjuvant PD-1 blockade in early stage lung cancer were presented by Patrick Forde, Sidney Kimmel Comprehensive Cancer Centre, Johns Hopkins University, Baltimore, US. Dr. Forde and colleagues conducted this study to determine the safety and feasibility of neoadjuvant nivolumab in 18 patients with stages I–IIIA non-small cell lung cancer (NSCLC). Patients received two doses of nivolumab at 4 and 2 weeks prior to surgical resection. Treatment was considered feasible if it did not delay surgery. Pathologic tumour response was the exploratory endpoint. Analyses of the pretreatment biopsy and post-treatment tumour samples, including programmed cell death ligand 1 (PD-L1) staining, multiplex immunohistochemical studies, and T-cell–receptor sequencing were also performed.

An exploratory analysis done in these patients exposed no significant safety concerns and no delays to surgery after neoadjuvant nivolumab. Importantly, 4 (22%) patients achieved radiologic responses, and 13 (72%) patients had stable disease, with just one patient experiencing progressive disease. Of 17 patients undergoing resection, 9 showed at least 50% regression of the tumour. Major pathologic responses after neoadjuvant treatment were reported in 7 (39%) patients, which means they had < 10% residual viable tumour at resection. One patient demonstrated pathologic complete response.

The relationship between response and PD-L1 expression remained unclear; although 3 patients with a robust response were positive for PD-L1 expression (≥ 1%) by immunohistochemical assay, one responder was PD-L1–negative, and one strongly PD-L1–positive patient did not respond to nivolumab. The tumours of responders showed dense infiltration of immune cells, with multiplex immunohistochemistry depicting infiltration of cytotoxic T cells into the tumours. New T-cell clones were detected in the post-treatment tumours that had not been seen in the pretreatment biopsy. Comprehensive genomic profiling had been completed for a small number of tumours that showed patients with major pathologic responses had higher absolute numbers of mutations. Absolute levels of predicted neoantigens were also higher in major responders.

Treatment-related toxicities were consistent with those seen in other studies of nivolumab, and there were no treatment-related deaths. Of 19 patients evaluated for safety, adverse events of any grade were reported by 32%; one (5%) patient had grade 3/4 toxicity leading to treatment discontinuation; however, the patient was still able to undergo surgery, which was uncomplicated.

Based on these results, the study is being expanded: One cohort will receive a third dose of nivolumab, and the other cohort will receive the combination of nivolumab and ipilimumab preoperatively. In addition, comprehensive genomic profiling, immunohistochemical, T-cell–receptor clonality, and tumour-infiltrating lymphocytes functionality studies are ongoing, and larger follow-up clinical studies are planned. NCT02259621. Forde *et al.* Abstract LBA41_PR

Practice point and future research opportunities

The study indicates that neoadjuvant administration of nivolumab is safe and feasible in stages I–IIIA NSCLC, and suggests that anti–PD-1 immunotherapy may have activity in early-stage disease. Nearly 40% of patients with early-stage NSCLC treated with two doses of nivolumab had major pathologic responses associated with immune cell infiltration of tumour, and these tumours could be downstaged prior to surgery. One explanation for this activity is that having tumour in situ means having more antigen present when the anti-PD1 is administered, which may be better than giving it in the adjuvant setting, where only micrometastases may be present with a small amount of antigen. However, there is a potential for bias when comparing a small biopsy, which might not represent the whole tumour, with the resected tumour.

Analysis indicates adjuvant may be more effective than neo-adjuvant chemotherapy with docetaxel plus carboplatin in resectable stage IB to IIIA NSCLC

Yi-Long Wu, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China, and colleagues located throughout China compared survival in patients receiving adjuvant versus neoadjuvant chemotherapy plus complete resection of stage II-IIIA NSCLC. The study enrolled patients with stage IB-IIIA NSCLC who were randomly assigned to 3 cycles adjuvant docetaxel at 75 mg/m^2, carboplatin at a dose providing AUC5 on day 1 every 3 weeks after resection or 3 cycles of neoadjuvant docetaxel/carboplatin at the same schedule followed by surgery within 6 weeks after chemotherapy. The primary endpoint was disease-free survival (DFS); secondary end points included 3- and 5-year overall survival (OS) and safety. Between March 2006 and May 2011, 214 patients were screened from 13 institutes; the planned sample size was 410 patients, which resulted in early closure of the trial due to slow accrual.

The screening yielded 198 eligible patients who were randomised to the neoadjuvant arm (n=97) or to the adjuvant arm. (n=101). The patients' median age was 58, 80.3% were male and 48.5% of patients had adenocarcinoma.

All patients completed neoadjuvant chemotherapy and 87.4% completed the adjuvant chemotherapy. The objective response rate was 34%, and 12.4% of patients showed disease progression. No statistically significant difference was observed in DFS at 3 and 5 years between treatments. The 3-year DFS rate was 56.0% in the adjuvant arm versus 43.0% in the neoadjuvant arm, hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.51-1.13 (p = 0.172), and the 5-year DFS was 50.0% with adjuvant versus 33.0% with neoadjuvant chemotherapy, HR 0.69; 95% CI 0.48, 1.00 (p = 0.051). The OS results showed an advantage that favoured adjuvant therapy. The 3-year OS was 68.0% versus 64.0%, HR 0.88; 95% CI 0.54,1.43 (p = 0.602), and 5-year OS was 60.0% versus 43.0%, HR 0.66; 95% CI 0.44,1.00 (p = 0.049) in the adjuvant versus neoadjuvant arms, respectively.

No unexpected toxicities were seen; 41.2% of patients experienced grade 3/4 neutropenia. One chemotherapy-related death occurred in the adjuvant arm and one patient died of perioperative pulmonary embolism in the neoadjuvant arm. NCT00321334. Wu *et al.* Abstract 1178O

Practice point and future research opportunities

A previous meta-analysis that indirectly compared adjuvant to neoadjuvant chemotherapy showed no difference in survival. This study adds information that favours adjuvant chemotherapy; a non-statistically significant trend towards improved DFS for adjuvant over neoadjuvant chemotherapy was seen in patients undergoing resection for NSCLC. The trend favouring adjuvant chemotherapy was reflected in the OS results where adjuvant chemotherapy became significantly superior to neo-adjuvant chemotherapy in the 5-year rates. More patients completed the full course of chemotherapy in the adjuvant than in the neoadjuvant group, which could also explain these results.

THORACIC MALIGNANCIES – NSCLC, Metastatic

PD-1 inhibition shows promise as first-line treatment in high PD-L1 expressing patients with advanced NSCLC

Martin Reck of the Lung Clinic Grosshansdorf in Grosshansdorf, Germany and colleagues throughout Europe conducted the phase III KEYNOTE-024 trial of first-line pembrolizumab in patients with tumours expressing levels ≥ 50% of PD-L1 who demonstrated a compelling survival advantage over patients receiving standard first-line platinum-based chemotherapy. The trial was halted early based upon a 45% objective response rate (ORR) and improved progression-free survival (PFS) of 4.3 months over chemotherapy. KEYNOTE-024 enrolled 305 patients having no treatable EGFR mutations or ALK translocations from 16 European countries. Patients were randomised to 35 cycles of 200 mg pembrolizumab (n=154) or to 4 to 6 cycles of investigator's choice of platinum-containing chemotherapy doublet (n= 151). Crossover from the chemotherapy arm at diseases progression was allowed. The study's primary end point was PFS and secondary end points included overall survival (OS), ORR, and safety.

An interim analysis done at a median follow-up of 11.2 months showed pembrolizumab-treated patients had median PFS of 10.3 months compared to 6.0 months with chemotherapy, hazard ratio [HR] 95% confidence interval [CI] 0.37, 0.68 ($p < 0.001$); 6-month PFS rates were 62% versus 50%) and 12-month PFS rates were 48% versus 15% with pembrolizumab versus chemotherapy, respectively. Median OS had had not been reached in either treatment group but the comparison favoured pembrolizumab; 6-month OS rates were 80% with pembrolizumab compared to 72% with chemotherapy, HR 0.60; 95% CI 0.41, 0.89, ($p = 0.005$). The OS rates were higher with pembrolizumab despite possibly being confounded by crossover of more than 40% from the chemotherapy arm after disease progression. Subgroup analysis revealed a consistent survival advantage with pembrolizumab across all subgroups excepting female-never smokers.

A lower incidence of any grade adverse events (AEs) of 73% was seen in the pembrolizumab arm versus 90% with chemotherapy. Grade 3/4 AEs were also more frequent in the chemotherapy arm, wherein 53% of patients reported an AE compared to 27% of patients receiving pembrolizumab. Study discontinuation due to AEs occurred in 7% of pembrolizumab and 11% of chemotherapy treated patients. One death in the pembrolizumab arm and 3 deaths in the chemotherapy arm were determined to be treatment-related. These results were simultaneously published online in *The New England Journal of Medicine* (NEJM). NCT02142738. EudraCT number 2014-000323-25. Reck *et al.* LBA8_PR; *NEJM* 2016; 375:1823-1833.

Practice point and future research opportunities

Pembrolizumab demonstrated PFS and OS that were superior to platinum-based chemotherapy

in patients with advanced NSCLC and tumours expressing PD-L1 levels ≥50%. Taken together with the safety profile, which showed a lower rate of treatment-related adverse events than chemotherapy, pembrolizumab may be considered as a new standard of care for first-line therapy in high PD-L1–expressing advanced NSCLC with no oncogenic driven disease. The patient population in this trial also had good performance status, no untreated brain metastases, no treatable oncogenic ALK or EGFR aberrations, and had not received prior steroid therapy. In daily clinical practice, perhaps 20% of patients with advanced NSCLC may have disease characteristics similar to this population. These data confirm findings from two previous KEYNOTE trials that also showed promising beneficial effects with pembrolizumab in patients with NSCLC and PD-L1-expression with the most favourable outcomes occurring in patients with tumours having high PD-L1 expression, which supports pembrolizumab over platinum-based chemotherapy as a new standard of care in this population. Further study is warranted to explore whether patients with lower levels of PD-L1 expression also derive more benefit from pembrolizumab than chemotherapy.

Atezolizumab in patients with NSCLC and disease progression following platinum-containing chemotherapy

Atezolizumab is a PD-L1 directed antibody that blocks PD-L1 binding to PD-1 and B7.1 while leaving the PD-L2/PD-1 interaction intact, thereby acting to restore tumour-specific T-cell immunity. Fabrice Barlesi, Aix-Marseille University and the Assistance Publique Hôpitaux de Marseille in Marseille, France presented the first results for a PD-L1 directed antibody from a primary efficacy analysis carried out in the first 850 of a total 1225 patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that had been previously treated with platinum-containing chemotherapies enrolled in the OAK study. The OAK is an ongoing randomised, global, multicentre, open-label phase III study, with the primary endpoint of overall survival (OS) and safety with atezolizumab as compared to the historical standard of care, docetaxel. The patients' median age was 64 years, 61% were male, 25% had received two prior lines of therapies, and 26% of patients' had squamous histology. All patients were stratified according to PD-L1 expression status, the number of prior chemotherapy regimens, and tumour histology then randomised to 1200 mg intravenous atezolizumab every 3 weeks or 75 mg/m^2 docetaxel every 3 weeks (425 patients per arm).

The overall intent to treat cohort, including patients with low to no PD-L1 expression, showed a 27% improvement in OS with atezolizumab compared to patients receiving docetaxel; median OS was 13.8 months versus 9.6 months, respectively, hazard ratio [HR] 0.73 (p = 0.0003).

When patients were stratified according to PD-L1 expression levels in the tumour or surrounding immune cells, OS was 59% greater among patients in the highest tertile of PD-L1 expression receiving atezolizumab, compared to patients with similar expression levels receiving docetaxel; the 16% of patients having ≥ 50% tumour cell or ≥ 10% immune cell PD-L1 expression receiving atezolizumab demonstrated median OS of 20.5 months compared with 8.9 months in the docetaxel arm, HR 0.41 (p < 0.0001). The median OS in 55% of patients having moderate PD-L1 expression ≥1% was 15.7 months with atezolizumab versus 10.3 months with docetaxel, HR 0.74 (p = 0.0102). Similar benefit was also seen in patients with low PD-L1 expression levels

(<1%) who demonstrated median OS of 12.6 with atezolizumab versus 8.9 months with docetaxel, HR 0.75 (p = 0.0205). Atezolizumab showed significant OS benefit across subgroups of age, PD-L1 status, and smoking status; however, patients harbouring active EGFR mutations showed no benefit. The OS benefit was observed among patients regardless of histology, although the magnitude of benefit was greater in patients with non-squamous histology where OS was 15.6 versus 11.2 months with atezolizumab versus docetaxel, respectively, HR 0.73, (p = 0.0015). Patients with squamous histology demonstrated OS of 8.9 versus 7.7 months with atezolizumab versus docetaxel, respectively, HR 0.77 (p = 0.0383).

Secondary endpoint results, including progression-free survival (PFS) per RECIST v1.1 were mixed, with patients overall receiving atezolizumab demonstrating numerically lower PFS of 2.8 months versus 4.0 months with docetaxel, HR 0.95 (p = 0.4928). The PFS benefit increased proportionally to higher PD-L1 expression, where median PFS of 4.2 months was observed in the atezolizumab arm compared to 3.3 months in the docetaxel arm. Similarly, the objective response rate (ORR) was 13.6% versus 13.4% in the overall atezolizumab versus docetaxel arms, respectively; however, the ORR was stronger in PD-L1 expressers, who achieved ORR of 31% with atezolizumab compared to 11% of docetaxel patients. The overall duration of response was 16.3 versus 6.2 months in the respective arms. No new safety signals emerged with ether treatment. There was a lower incidence of adverse events (AEs) with atezolizumab than docetaxel; treatment-related AEs grades 3/4 occurred in 15% and 43% of patients receiving atezolizumab and docetaxel, respectively. No deaths occurred with atezolizumab and one death related to docetaxel occurred. The results were published in the *Lancet*. NCT02008227. Barlesi *et al.* LBA44_PR; *Lancet* 2017;389(10066):255-265.

Practice point and future research opportunities

Findings from the first phase III study of atezolizumab confirm the efficacy seen in the POPLAR phase II study. Treatment with atezolizumab resulted in a statistically significant and clinically relevant improvement in OS compared with the current second and third line standard treatment of docetaxel in NSCLC. An improvement in OS was observed even in patients with no PD-L1 expression, therefore PD-L1 negativity cannot be used as an exclusion factor for treatment. Atezolizumab demonstrated a favourable safety profile that appears to be similar to that of other immune-checkpoint inhibitors. Atezolizumab offers a new second-line therapeutic strategy for patients with NSCLC, regardless of the PD-L1 status of the tumour and surrounding immune cells. Since the aim of atezolizumab therapy is to allow the immune system to control and eliminate cancer calls, further investigation of atezolizumab in different types of cancer may be warranted.

Based upon results from the phase III OAK and phase II POPLAR studies, in October, 2016 the US Food and Drug Administration (FDA) approved atezolizumab for the treatment of metastatic NSCLC in patients who have disease progression on platinum-containing chemotherapy, or have progressed on an appropriate FDA-approved targeted therapy if the tumour has EGFR or ALK gene abnormalities.

Second-line ceritinib in crizotinib pre-treated ALK positive NSCLC

Giorgio Scagliotti, Department of Oncology, University of Turin, Turin, Italy and colleagues, conducted ASCEND-5, an open label multicentre, phase III study in 231 patients with advanced ALK-positive NSCLC who had progressed following crizotinib. The ASCEND-5 compared ceritinib to chemotherapy, the current second-line standard in that setting. Patients were randomised to daily ceritinib at 750 mg (n = 115) or the investigator's choice of chemotherapy, pemetrexed at 500 mg/m^2 (n=40), or 75 mg/m^2 docetaxel (n=73). Brain metastases at baseline were reported in 65 (56.5%) and 69 (59.5%) patients in the ceritinib and chemotherapy arms, respectively. Crossover to ceritinib was allowed upon disease progression. The primary endpoint was progression-free survival (PFS), as assessed by a blinded independent review committee (BIRC).

The PFS was more than 3 times longer with ceritinib than with chemotherapy; patients with ALK-positive NSCLC had significantly longer median PFS of 5.4 months with ceritinib compared to 1.6 months with chemotherapy, hazard ratio [HR] 0.49 ($p < 0.001$). Overall survival (OS) was possibly confounded by the crossover of 75 patients to ceritinib. Similar median OS of 18.1 months with ceritinib versus 20.1 months with chemotherapy was observed. The objective response rate by BIRC was 39.1% with ceritinib versus 6.9% with chemotherapy; complete or partial response was achieved by 45 ceritinib versus 8 chemotherapy patients. The disease control rates were 75.5% versus 36.2% with ceritinib versus chemotherapy, respectively.

Toxicities were similar to previously reported studies. The most frequent grade 3/4 adverse events with ceritinib were nausea (7.8%), vomiting (7.8%) and diarrhoea (4.3%), and with chemotherapy grade 3/4 neutropenia occurred in 15.5%, fatigue in 4.4%, and nausea occurred in 1.8% of patients. Patient-reported outcomes, including lung cancer-specific symptoms and overall health status, showed symptom improvement with ceritinib over placebo ($p < 0.05$); however, two scales for gastrointestinal symptoms showed deterioration. NCT01828112. Scagliotti *et al.* LBA42_PR

Practice point and future research opportunities

The majority of patients treated with the current standard first line treatment for NSCLC, crizotinib, develop resistance due to ALK rearrangement, making a more effective second line agent a priority. This was the first phase III study to assess whether the second generation ALK inhibitor ceritinib is superior to chemotherapy upon progression on crizotinib therapy in NSCLC. Significantly improved PFS and response rates were observed with ceritinib over standard chemotherapy. No improvement in OS was seen with ceritinib, possibly due to the crossover at progression of over two-thirds of patients receiving chemotherapy. Single arm studies have suggested that ceritinib could be a standard option in the second line setting after crizotinib has failed. The positive effect on PFS in this phase III study confirms that there is greater benefit using a second ALK inhibitor over standard chemotherapy. This will establish sequential crizotinib followed by a second generation ALK inhibitor as the standard treatment for patients with metastatic ALK-positive NSCLC.

Nivolumab does not improve survival over platinum-based doublet chemotherapy as first-line therapy in advanced NSCLC despite PD-L1 tumour expression in phase III trial

Mark A. Socinski, Florida Hospital Cancer Institute, USA presented findings from the phase III CheckMate 026 trial investigating the efficacy of first-line treatment with nivolumab compared to platinum-based doublet chemotherapy in 541 patients with histologically confirmed and previously untreated stage IV or recurrent NSCLC and PD-L1 positive tumours (defined as present in 1% or more tumour cells). The patients were randomised 1:1 to receive nivolumab at 3 mg/kg i.v. every 2 weeks or to platinum-based doublet chemotherapy every 3 weeks for up to 6 cycles until disease progression or unacceptable toxicity. Patients in the chemotherapy arm were allowed to crossover to nivolumab upon progression. Patients with EGFR activating mutations and ALK translocations, which are sensitive to targeted therapy, were excluded. The primary endpoint was progression-free survival (PFS), assessed by an independent radiology review committee in patients with PD-L1 in 5% or more tumour cells.

In a subgroup of 423 patients with 5% or greater PD-L1 expression, PFS was 4.2 months with nivolumab and 5.9 months with chemotherapy, hazard ratio [HR] 1.15; 95% confidence interval [CI] 0.91 (1.45, p = 0.25). Overall survival (OS) was 14.4 months for nivolumab versus 13.2 months for chemotherapy, HR 1.02; 95% CI 0.80, 1.30.

There were no new safety signals with nivolumab and it demonstrated far less toxicity than chemotherapy. Among all treated patients, any and serious treatment-related adverse events were 71% and 18% with nivolumab versus 92% and 51% with chemotherapy, respectively. NCT02041533. Socinski *et al.* LBA7_PR

Practice point and future research opportunities

Nivolumab represents a standard of care as second-line treatment of advanced NSCLC as it improved OS compared to docetaxel in phase III trials, and nivolumab showed a promising response rate in a phase I trial in advanced NSCLC patients with 1% or greater PD-L1 expression in their tumour cells in the first-line setting. However, nivolumab did not show superior survival compared to platinum-based chemotherapy as first-line therapy in stage IV/recurrent NSCLC patients with ≥5% PD-L1 tumour expression. There are a number of possible reasons for the disappointing PFS results, but regarding OS, there was a high rate of crossover to immunotherapy on the chemotherapy arm. Also, OS in the chemotherapy arm was better than historical standards. The investigators are conducting further analyses to evaluate these results.

More research is needed about how to use the PD-L1 biomarker to select patients for treatment with nivolumab. In addition, phase I studies suggest that combination immunotherapy improves response rate and outcome, but at the expense of increased toxicity, compared to single agent immunotherapy in NSCLC. Thus, it will be important to investigate this strategy further.

SELECT-1 trial of selumetinib in patients with KRAS-mutant NSCLC did not meet primary endpoint

Principal investigators Pasi Jänne, Dana-Farber Cancer Institute, Boston, US, presented findings from the phase III SELECT-1 trial of the MEK 1/2 inhibitor, selumetinib, in combination with docetaxel chemotherapy as second-line treatment in patients with KRAS mutation-positive locally-advanced or metastatic non-small cell lung cancer (NSCLC). The SELECT-1 was an international trial with 510 randomised patients in over 200 centres. Patients received either oral selumetinib at 75 mg twice daily or placebo in combination with docetaxel, administered intravenously at 75 mg/m^2 on day 1 of every 21-day cycle.

The results showed that the trial did not meet its primary endpoint of progression-free survival (PFS), and selumetinib did not have a significant effect on overall survival (OS). Median PFS was 3.9 months with selumetinib compared to 2.8 months with placebo, hazard ratio [HR] 0.93 (2-sided p = 0.44) and median OS was 8.7 months versus 7.9 months in the respective groups, HR 1.05 (2-sided p = 0.64). There was a trend towards a higher objective response rate with selumetinib compared to placebo of 20.1% versus 13.7%, respectively, odds ratio 1.61 (p = 0.051).

The adverse event (AE) profiles for selumetinib and docetaxel were consistent with those seen previously. Serious AEs occurred more frequently at 49% in patients treated with the selumetinib plus docetaxel combination compared to 32% with placebo, as did AEs leading to hospitalisation, which occurred in 46% of selumetinib versus 30% of placebo patients. NCT01933932. Jänne *et al.* LBA47_PR

Practice point and future research opportunities

Although a randomised phase II trial showed promising activity of selumetinib in combination with docetaxel in patients with KRAS mutation-positive NSCLC, these results were not confirmed in the phase III SELECT trial. This trial demonstrated that the addition of selumetinib to docetaxel in patients with advanced KRAS mutant NSCLC does not provide clinical benefit in terms of improving PFS or OS; therefore, it is not a treatment approach that should be taken forward.

There remains a desperate need to develop new treatments for the subset of NSCLC patients with KRAS-mutant lung cancer, which is the largest genomically defined subset of NSCLC where there are no effective targeted therapies. Selumetinib inhibits an effector protein immediately downstream from KRAS, which was thought to turn off KRAS-mediated signalling in these cancers.

Selumetinib was granted Orphan Drug Designation by the US Food and Drug Administration for adjuvant treatment of patients with stage III or IV differentiated thyroid cancer.

The SUNRISE phase III trial of bavituximab plus docetaxel in patients with previously treated stage IIIb/IV non-squamous NSCLC is halted after futility analysis

David Spigel, Oncology, Sarah Cannon Research Institute-cancer centre, Nashville, USA, presented the phase III SUNRISE trial comparing bavituximab plus docetaxel with docetaxel and placebo for patients with non–small cell lung cancer (NSCLC), which was halted after a futility analysis. Bavituximab is an IgG3 monoclonal antibody that binds to anionic phospholipids to inhibit tumour growth by stimulating antibody-dependent cellular cytotoxicity.

In SUNRISE, 582 patients with stage IIIb/IV non-squamous NSCLC who progressed after standard frontline treatment were randomised in a 1:1 ratio to bavituximab plus docetaxel or docetaxel plus placebo. Patients in each arm received up to six 21-day cycles of docetaxel at 75 mg/m^2 followed by weekly bavituximab at 3 mg/kg or placebo. Median overall survival (OS) was 10.7 months (95% confidence interval [CI] 8.6,11.5) among 297 patients receiving bavituximab/docetaxel and 10.8 months (95% CI, 9.2, 12.6) with placebo/docetaxel. The prespecified analysis was conducted after 33% of events and an Independent Data Monitoring Committee found that the combination of bavituximab and docetaxel failed to improve OS compared with docetaxel and placebo, the trial's primary endpoint, for patients with previously treated locally advanced or metastatic non-squamous NSCLC. The safety profile was generally similar between the groups, although the rate of grade 3/4 febrile neutropenia was slightly higher at 8.75% with bavituximab/docetaxel versus 5.69% with docetaxel/placebo. NCT01999673. Spigel *et al.* LBA45

Practice point and future research opportunities

A prior, similarly designed phase II trial demonstrated median OS of 11.7 months with bavituximab/and docetaxel compared with 7.3 months with docetaxel/placebo; this study, plus historical data for docetaxel, set the bar for survival expectations in the phase III study. However, the SUNRISE phase III trial did not meet the primary objective of superior OS in patients with previously treated non-squamous NSCLC.

The developing company has planned future trials in HER2-negative and triple negative breast but has placed all bavituximab/chemotherapy combination studies in NSCLC on hold.

Pembrolizumab added to first-line chemotherapy improves outcomes in advanced NSCLC

Corey Langer, Thoracic Oncology Program, Abramson Cancer Center, University of Pennsylvania, USA presented findings from cohort G of the multicentre, open-label, phase II KEYNOTE-021 study, which randomised 123 chemotherapy-naive patients with stage IIIB/IV, non-squamous non-small-cell lung cancer (NSCLC) containing no EGFR or ALK targetable

mutations, to receive four cycles of carboplatin to an area under the curve of 5 mg/mL per minute and pemetrexed at 500 mg/m^2 every three weeks, or to the same regimen plus pembrolizumab at 200 mg every three weeks.

After a median follow-up of 10.6 months, an objective response by RECIST was seen in 55% of 60 patients receiving additional pembrolizumab compared to 29% of the 63 patients receiving chemotherapy alone (p = 0.0016), yielding a significant estimated treatment difference of 26%. The response with pembrolizumab was rapid, occurring after a median of 1.5 months versus 2.7 months with chemotherapy. Both responses were durable, with a respective 88% and 78% of responders in each group still alive and progression-free at the time of data cut-off. Overall survival rates were similar between groups where a 6-month survival rate of 92% was observed in each arm.

When patients receiving pembrolizumab were assessed by PD-L1 expression levels in their tumour, the investigators noticed a higher response rate of approximately 80% in patients with tumours having PD-L1 expression greater than or equal to 50%.

A higher incidence of adverse events (AEs) of grade 3 severity or above was observed in the pembrolizumab arm compared to the chemotherapy alone arm (39% versus 26%). However, treatment discontinuation rates were similar between groups at 10% for the pembrolizumab arm compared to 13% for the chemotherapy only arm. The most common treatment-related AEs were fatigue and nausea, which were more common in patients receiving pembrolizumab, and anaemia, which was more common in the chemotherapy alone arm. The results presented at ESMO 2016 were published simultaneously online in *The Lancet Oncology*. NCT02039674. Langer *et al.* LBA46_PR; *Lancet Oncology* 2016;17(11):1497-1508.

Practice point and future research opportunities

KEYNOTE-021 is the first randomised phase II trial in advanced, treatment-naive non-squamous NSCLC to assess the benefit of adding a monoclonal antibody targeting PD-1 to standard chemotherapy and the results indicate that adding pembrolizumab to carboplatin and pemetrexed chemotherapy could be an effective strategy for the first-line treatment of advanced, non-squamous NSCLC. The safety and efficacy of adding pembrolizumab to first-line platinum-based chemotherapy for advanced non-squamous NSCLC is being further assessed in the KEYNOTE-189 and KEYNOTE-047 trials. If these benefits reported here are confirmed in an ongoing phase III trial, the first-line treatment paradigm in advanced NSCLC could be altered to include pembrolizumab.

Data from long-term follow-up of KEYNOTE-010 study with pembrolizumab in previously treated advanced NSCLC

Roy S. Herbst, Medical Oncology, Yale Cancer Center, Smilow Cancer Hospital, Yale School of Medicine, New Haven, USA, presented updated findings on behalf of colleagues from the KEYNOTE-010 trial of first line pembrolizumab versus docetaxel from a 6-month extended follow-up. KEYNOTE-010 has already demonstrated superior overall survival (OS) over

docetaxel in patients with previously treated advanced non-small cell lung cancer (NSCLC). The trial randomised 1034 patients with NSCLC and TPS ≥1% that progressed on 2 or more courses of platinum-doublet chemotherapy to pembrolizumab at 2 or 10 mg/kg every 3 weeks or docetaxel at 75 mg/m^2 every 3 weeks. Crossover upon progression was not permitted until December, 2015.

As of March 31, 2016, the median follow-up was 19.2 months and median exposure was 106 days with pembrolizumab at both doses versus 62 days with docetaxel. Pembrolizumab continued to show superior OS that was similar between doses. The 18-month OS rates were 37% with pembrolizumab at 2 mg/kg, 43% at 10 mg/kg versus 24% with docetaxel in patients having TPS ≥1% and 46%, 52%, and 24%, respectively for TPS ≥50%. Median OS in TPS ≥1% at low and high doses of pembrolizumab versus docetaxel were 10.5 and 13.6 versus 8.6, respectively, hazard ratio [HR] 0.7 (2 mg/kg and HR 0.60 (10 mg/kg). In the TPS ≥50% group, median OS was 15.8 months HR 0.54 and 18.8 months, HR 0.48 versus 8.2 months in the respective treatment arms. The objective response rate was also higher for TPS ≥1% (19% and 20% versus 10%) and ≥50% (29% and 32% versus 9%). At this time-point, 60% of pembrolizumab versus 15% of docetaxel responders in the overall cohort, were alive, and progression free.

Treatment-related adverse event (AE) rates any grade remained lower with pembrolizumab at 64% and 67% versus 81% with docetaxel, as well as grade 3 to 5 AEs of 13% and 17% versus 36% in the respective arms. NCT01905657; EudraCT number 2012-004391-19. Herbst *et al.* LBA48

Practice point and future research opportunities

These and previously reported data formed the basis for the FDA granting a breakthrough therapy designation to pembrolizumab for the treatment of patients with NSCLC who are EGFR mutation- or ALK rearrangement-negative and whose disease has progressed on, or following, platinum-based chemotherapy. Pembrolizumab, a humanised IgG4 PD-1 blocking antibody that exerts dual ligand blockade of the pathway, was previously granted breakthrough status for advanced melanoma, and is being studied across more than 30 types of cancers as monotherapy and in combination. The superior OS for pembrolizumab over docetaxel in patients with previously treated, PD-L1–expressing advanced NSCLC was confirmed in this longer follow-up, as was the lack of difference between pembrolizumab doses, and the durability responses. Taken together with the favourable safety profile despite longer exposure, these data support pembrolizumab as a standard of care for previously treated, PD-L1–expressing, EGFR- and ALK-negative NSCLC.

Continuing gefitinib plus chemotherapy in EGFR mutation-positive NSCLC after progression on first-line gefitinib has deleterious survival effect

Jean-Charles Soria, Department of Medicine, Institut de Cancérologie Gustave Roussy, Villejuif, France reported findings from the final overall survival (OS) analysis of the IMPRESS trial, which evaluated the possible benefit of continuing gefitinib plus cisplatin/pemetrexed versus placebo plus cisplatin/pemetrexed in patients with acquired resistance to first-line gefitinib. Professor Soria and colleagues randomised 265 adult chemotherapy-naive patients with locally advanced/metastatic NSCLC and activating EGFR mutation that progressed on first-line gefitinib to gefitinib at 250 mg/day or placebo, each in combination with cisplatin 75 mg/m^2/pemetrexed 500 mg/m^2. The primary endpoint was progression-free survival (PFS) and secondary endpoints included OS and safety/tolerability. Primary PFS results confirmed that continuing gefitinib in addition to chemotherapy has little clinical benefit.

A total of 133 patients in the gefitinib and 132 patients in the placebo arms were followed until November, 2015 when 175 (66%) patients had died; most deaths, 65% of gefitinib and 55% with placebo, were due to disease progression. Continuation of gefitinib versus placebo plus cisplatin/pemetrexed was detrimental to OS, hazard ratio [HR] 1.44 (p = 0.016).

A biomarker analyses had been preplanned for EGFR T790M mutation status using plasma circulating free tumour-derived DNA. Subgroup analysis by plasma T790M mutation status showed OS of 10.8 versus 14.1 months, HR 1.49 for T790M-positive, and 21.4 versus 22.5 months, HR 1.15 for T790M-negative with gefitinib versus placebo, respectively. More patients (71%) in the placebo arm received post-discontinuation therapy compared to 61% of patients in the gefitinib arm. Gefitinib plus cisplatin/pemetrexed continued to be well tolerated, with no new unexpected safety findings. NCT01544179. Soria *et al.* Abstract 1201O

Practice point and future research opportunities

Although it had been postulated that continuing gefitinib after disease progression could be beneficial as there are multiple causes of acquired resistance to EGFR tyrosine kinase inhibitors and some sites of tumour metastases could continue to be sensitive to treatment, final IMPRESS overall survival data confirm the results published in the *Lancet Oncology* (http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00121-7/abstract). The final results from this phase III trial indicate that patients with acquired resistance to first-line gefitinib should not continue to receive gefitinib plus doublet chemotherapy beyond progression, due to the observed detrimental effect on OS.

Analysis of the clinical and biological characteristics of EGFR-mutated NSCLC

Charlotte Leduc, Pneumologie, C.H.U. Strasbourg-Nouvel Hopital Civil, Strasbourg, France, presented findings on behalf of the French Cooperative Thoracic Intergroup from a large analysis of a database containing 17,664 patients. The investigators identified 1837 (10.3%) patients with EGFR mutated non-small cell lung cancer (NSCLC) that were evaluated for biological and clinical characteristics. In this large sample set, EGFR exon 18, 19, 20 and 21 mutations were

found in 102 (5.6%), 931 (50.6%), 102 (5.6%), and 702 (38.2%) patients; of these, 70 had never been described. Smokers showed more frequent mutation in exon 18 (20%) and exon 20 (19%) compared to exon 19 (11%) and 21 (11%) (p = 0.002). T790M mutated patients (n=42) were excluded from the survival analysis.

After a median follow-up of 36.7 (range: 36.4 to 37) months, median overall survival (OS), first-line progression-free survivals (PFS) and disease control rates (DCR) after treatment with a first-line EGFR tyrosine kinase inhibitor (TKI) according to the type of EGFR mutation were analysed. Median OS was 11.8 months in the population of 1270 EGFR wild-type patients; however, OS was prolonged in 555 patients with exon 19 deletions to 26.5 months compared to 21.3 months in 439 patients with L858R mutations (p = 0.045). In exon 19, there was no difference in OS based on the length of the deletion. Regarding exon 21, median OS was longer for patients harbouring L858R mutations at 22.4 months versus 14.1 months in patients with L861Q and 14.9 months in patients with other substitutions or 11.8 months in patients with wild-type (p < 0.0001). The DCR following treatment with a first-line EGFR-TKI was 82%, 77%, and 54.5% for common, rare and complex mutations, respectively (p = 0.05). No difference in DCR was observed with EGFR TKI based on the type of mutation in exon 19 or in exon 21. NCT01700582. Leduc *et al.* Abstract 1202O

Practice point and future research opportunities

This large analysis identified common and non-common EGFR mutations and elucidated the different clinical characteristics. Among common mutations, exon 19 mutated patients experienced better outcomes compared to other mutations and wild-type following treatment with an EGFR TKI.

Lenvatinib shows promise in patients with RET fusion-positive adenocarcinoma of the lung

Approximately 1% to 2% of patients with lung adenocarcinoma have tumours that harbour RET fusions that activate RET kinase, prompting Vamsidhar Velcheti, Taussig Cancer Institute, Cleveland Clinic in Cleveland, USA and colleagues to investigate the efficacy of lenvatinib, a multikinase inhibitor with activity to RET, in an open label, phase II trial. The study enrolled 25 patients with RET-positive lung adenocarcinoma, who were treated with lenvatinib at 24 mg per day in 28-day cycles until disease progression or unacceptable toxicity occurred. Previously treated patients were eligible for enrolment, including those receiving prior RET-targeted therapy. KIF5B-RET fusion was seen in 13 patients and 12 patients had other RET fusion. Just 2 (8%) patients had received no prior treatment; 15 (60%) patients received ≥2 prior lines of therapy, and 7 (28%) patients had received prior RET therapy. The smoking status of the cohort included 16 (64%) never smokers, one (4%) current smoker, 7 (28%) former smokers, and one (4%) patient with unknown status. The primary endpoint of the trial was objective response rate (ORR) and secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR) defined as complete response (CR) plus partial response (PR) plus

stable disease (SD lasting for ≥ 7 weeks), clinical benefit rate (CBR) defined as CR plus PR plus durable SD (SD lasting for ≥23 weeks), and safety.

The primary endpoint, ORR was 16% and consisted entirely of confirmed PRs in 4 patients. The majority of patients experienced tumour shrinkage with lenvatinib and the DCR was 76% (19 patients). Of these, 12 maintained a durable response for 23 or more weeks, yielding a CBR of 48%. Median PFS in the entire study group was 7.3 months (95% confidence interval [CI] 3.6, 10.2 months). Median OS was not reached (95% CI 5.8 months, NE).

Subgroup analysis revealed that the 7 patients previously treated with a RET therapy showed the greatest response. In this cohort, the ORR was 14%, DCR was 86%, and CBR was 57% compared with 17%, 72%, and 44%, respectively, in patients not receiving prior RET inhibitors.

Lenvatinib demonstrated an acceptable safety profile; the most commonly reported treatment-emergent adverse events (TEAEs) were hypertension, which occurred in 68% of patients, nausea in 60%, decreased appetite and diarrhoea, each occurring in 52%, proteinuria in 48%, and vomiting in 44% of patients. TEAEs grade 3 or higher were reported in 23 (92%) patients. TEAEs requiring drug withdrawal occurred in 5 (20%) patients, dose reduction in 16 (64%), and dose interruption occurred in 19 (76%) patients. Three deaths due to AEs occurred on study; one death from pneumonia was possibly related to lenvatinib. NCT01877083. Velcheti *et al.* Abstract 1204PD

Practice point and future research opportunities

RET fusions are detected in 1% to 2% of lung adenocarcinoma and a number of genes, including KIF5B, CCDC6, NCO4 and TRIMM33, can act as fusion partners. Lenvatinib is oral multikinase inhibitor of VEGFR 1–3, FGFR 1–4, PDGFR–alpha, and RET and KIT proto-oncogenes.

In this trial, lenvatinib showed promising clinical activity in patients with RET-positive NSCLC with most patients demonstrating tumour shrinkage and disease control; toxicities were manageable in most patients with dose modification. These results support further evaluation of lenvatinib as a potential treatment for patients with RET-positive fusion-positive adenocarcinoma of the lung.

Comprehensive genomic profiling identifies targetable genomic alterations and high mutational burden in lung sarcomatoid carcinoma

Lung sarcomatoid carcinoma (LSC) is a rare, clinically aggressive, heterogeneous and poorly differentiated subtype that involves 3% to 4% of patients with non-small cell lung cancer (NSCLC). LSC is typically difficult to diagnose and is resistant to conventional therapies. LSC harbours a recurrent abnormality known as MET exon 14 skipping mutation that leads to loss of a particular amino acid that is critical to the binding of second protein, which then marks the first protein for degradation. This leads to a drive in cancer growth, according to Balazs Halmos, Clinical Cancer Genomics, Montefiore Medical Center, New York, USA. Dr. Halmos and colleagues queried whether comprehensive genomic profiling (CGP) could identify mutations in LSC that would be susceptible to novel targeted therapies. The investigators performed hybrid-

capture based CGP on 6,923 consecutive FFPE NSCLC samples obtained during the course of clinical care that identified 91 (1.3%) LSCs. The patients in this series had a median age of 67 years (range: 32 to 86), 59% were male, and 82% of tumours were stage IV.

The investigators found that 57% of LSC cases involved a genomic alteration (GA) and 34% of GA involved KRAS. Other GAs were identified in the 7 genes now recommended for testing in the NSCLC National Comprehensive Cancer Network (NCCN) guidelines that included 8.8% in MET, 7.7% BRAF, 6.6% EGFR, 2.2% ERBB2 or 1.1% in RET. No alterations were detected in ALK or ROS1. BRAF alterations included amplification and mutation at V600 or G469. EGFR alterations included amplification, exon 19 deletion, exon 20 insertion, and activating L858R mutation. Notably, MET exon 14 skipping alterations were enriched in this series in 7 (7.7%) samples compared to non-LSC NSCLCs which demonstrated an incidence of 2.8%.

In 39 cases that were wild-type for the 7 NCCN genes and KRAS, potentially actionable GAs were most commonly detected in PTEN at an incidence of 10.3%, PIK3CA at 7.7%, FGFR1 at 7.7%, and in PDGFRA at 7.7%. The median tumour mutation burden (TMB) was 8 mutations/megabase (range: 0 to 165, mean: 14), and 19 (21%) of cases had high TMB ≥ 20.

Clinical outcomes were available for a subset of patients that revealed 4 patients with LSC whose tumours harboured alterations in MET, BRAF, and EGFR that received targeted therapies demonstrated clinical benefit and one patient with TMB of 31 has an ongoing response to anti-PD-1 therapy. Halmos *et al.* Abstract 1212PD

Practice point and future research opportunities

This study demonstrated that CGP can be used to inform treatment options in patients with rare, and difficult to treat LSC. Targetable genetic alterations, including MET exon 14 alterations, were found in a majority of LSC patients, some of which occur at greater frequency than that observed in non-LSC NSCLCs. An important portion of LSC cases had high TMB, which suggests an increased likelihood of response to immunotherapy. Thus, CGP can lead to selection of appropriate targeted therapies in this population of patients, which has historically been poorly characterised and difficult to treat.

S-1 is non-inferior to docetaxel in patients with NSCLC who have received a platinum-based treatment

Lead author Makoto Nishio, Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan and colleagues conducted this large phase III trial to demonstrate the non-inferiority of S-1 monotherapy to docetaxel in 1154 patients with previously treated non-small cell lung cancer (NSCLC) in Asia. The study enrolled patients with stage IIIB/IV NSCLC who had received at least one regimen of platinum-based chemotherapy with/without prior exposure to gefitinib or erlotinib. Patients were randomly assigned to S-1 at 80 to 120 mg/day on days 1-28 of a 42-day cycle or to receive docetaxel at

60 mg/m^2 in Japan, or 75 mg/m^2 in other countries, on day one of a 21 day cycle. The primary objective was to evaluate whether S-1 is non-inferior to docetaxel in terms of overall survival (OS) and secondary objectives included progression-free survival (PFS), time to treatment failure (TTF), response rate (RR), quality of life, and safety.

At a median follow-up time of 30.75 months, the study satisfied the primary endpoint criteria and found that the median OS of the S-1 group of 12.7 months was non-inferior to 12.5 months with docetaxel, hazard ratio [HR] 0.945; 95% confidence interval [CI] 0.833, 1.073 (p = 0.3818). Similar PFS was demonstrated of 2.86 months with S-1 versus 2.89 months with docetaxel. The investigators did an analysis of response in Japan versus non-Japan, which also demonstrated similar response with S-1 and docetaxel in Japanese and non-Japanese patent populations (HR 0.9; P 0.3374). Grade 3 or higher febrile neutropenia and neutropenia were higher with S-1 at 0.9% and 13.6% with S-1 versus 5.4% and 47.7% with docetaxel. Other non-haematologic toxicities in the S1 and docetaxel groups included, diarrhoea (37.2% versus 18.2%), stomatitis (23.9% versus 14.5%), and decreased appetite (52.6% versus 37.9%), respectively. Nishio *et al.* Abstract 1218PD

Practice point and future research opportunities

This study demonstrated that S-1 is non-inferior to docetaxel in terms of OS and also demonstrated tolerable toxicity. S-1 monotherapy is one of treatment options for patients previously treated with platinum-based chemotherapy for NSCLC.

SMALL CELL LUNG CANCER

Alisertib (MLN8237) plus paclitaxel improves PFS over placebo plus paclitaxel as second line therapy for SCLC

Alisertib is an aurora A kinase inhibitor that has already been shown to have antitumor activity in patients with solid tumours, including those with small cell lung cancer (SCLC), explained Taofeek Owonikoko, Department of medical oncology, Emory University, Atlanta, USA. With colleagues, Dr. Owonikoko evaluated the efficacy and safety of alisertib combined with paclitaxel, compared to placebo plus paclitaxel in patients with SCLC who had relapsed within 6 months or did not respond to standard first-line, platinum-based chemotherapy. In the phase II trial, 178 patients were randomised 1:1 to receive alisertib orally at 40 mg, twice-daily on days 1-3, 8-10, and 15-17 and paclitaxel, which was administered intravenously at 60 mg/m^2 on days 1, 8, 15, or to treatment with a matched placebo plus paclitaxel given on the same days but at a dose of 80 mg/m^2. The patients had a mean age of 62 years, and just over half (57%) were men.

The primary endpoint was progression-free survival (PFS), as assessed by stratified log-rank test.

The analysis of PFS using IVRS stratification showed a median PFS of 101 with alisertib/paclitaxel versus 66 days with placebo/paclitaxel, hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.557, 1.067 (p = 0.113). The analysis for PFS using the corrected stratification factors again favoured alisertib/paclitaxel (HR 0.72; p = 0.038). Numerically higher objective response rate (ORR) of 22% versus 18%, disease control rates of 77% versus 67%, and overall survival (OS) of 6.87 versus 5.58 months also were seen with the alisertib/paclitaxel over placebo/paclitaxel, respectively, although statistical significance was not reached. Stable disease was achieved by 55% of patients receiving added alisertib compared to 49% of control patients and progressive disease occurred in 15% versus 26% of patients in the respective treatment arms.

Additional toxicities were observed with the combination treatment. Almost all (99% versus 96%) of patients reported some type of adverse event (AE), of which 75% and 51% were grade 3 or higher, respectively in the alisertib and placebo groups. Common any-grade AEs with the respective treatments were diarrhea (59% versus. 20%), neutropenia (49% versus 8%), anaemia (44% versus. 20%), and fatigue (44% versus 33%). Drug-related serious AEs were reported in 32% versus 7% and treatment discontinuation due to an AE was reported in 15% versus 6% of patients receiving alisertib/paclitaxel versus placebo/paclitaxel, respectively. NCT02038647; EudraCT 2013-003713-18 Owonikoko *et al.* Abstract 1423O

Practice point and future research opportunities

The treatment of SCLC, particularly in the second-line setting, remains challenging, and there are no targeted agents approved for use. When first-line therapies fail, the guideline-

recommended option is to put patients back on platinum-based chemotherapy if they were sensitive to this chemotherapy. Alisertib/paclitaxel demonstrated improved PFS over placebo/paclitaxel and similar favourable trends was observed for OS and the ORR, in this trial. This combination may be a possible option to topotecan for patients who progress on platinum-based chemotherapy that warrants further investigation.

SCLC harbours targetable alterations including MYCL1 fusions that respond to alisertib

Siraj Ali, Clinical Development, Foundation Medicine, Inc., Cambridge, USA, and colleagues used comprehensive genomic profiling (CGP) to assays 689 small-cell lung cancer (SCLC) cases with the aim of detecting targetable genomic alterations to improve treatment options for patients progressing on platin/etoposide. The investigators used hybrid-capture based CGP during the course of clinical care to identify all 4 classes of genomic alterations (GA), base substitutions, short insertions/deletions, copy number alterations, and fusions to suggest possible benefit from targeted therapy. The patients in this series had a median age of 62 years, and 50% were female.

The investigators found the most commonly altered genes were TP53 in 91% of samples, RB in 68%, MLL2 in 13%, LRP1B in 11%, RICTOR in 11% and FGF10 in 9% of cases. MYCL1 amplification was identified in 53 cases, and 6 MYCL1 fusions arising from inter-chromosomal rearrangements were detected, including MYCL1-COL9A2, MYCL1-MSRB2, MYCL1-PABPC4, MYCL1-MACF1, MYCL1-JAZF1, and one MYCl1 with an indeterminate partner. Other rearrangements of cancer relevant genes that were detected included 3 cases of c-MYC rearrangements co-occurring with MYC amplification, three cases of RICTOR rearrangements, and one case each of BRD4-NOTCH3 and EML4-ALK.

One never smoker, 46-year old male was diagnosed with SCLC, which harboured MYCL1-JAZF1 that was detected on CGP. Therefore, he was treated with alisertib and demonstrated an 18-month nearly complete response after failing 3 previous lines of chemotherapy. Ali *et al.* Abstract 1424O

Practice point and future research opportunities

This study identified 6 novel MYCL1 fusions that may be targetable by existing therapies, such as the investigational aurora kinase inhibitor, alisertib, which is hypothesised to target MYCL downstream pathways. In light of the response of the index patient to alisertib, further focused investigation of MYCL1 and other fusions in SCLC is warranted to assess possible oncogenic drivers and targetable genetic alterations.

THORACIC MALIGNANCIES - OTHER

NGR-hTNF added to best investigator choice of treatment demonstrates activity in previously treated patients with malignant pleural mesothelioma

Vanessa Gregorc, Department of Oncology, San Raffaele Scientific Institute, Milan, Italy, reported findings from the phase III NGR015 trial of NGR-hTNF, a recombinant protein derived from the fusion between a peptide and human tumour necrosis factor alpha (TNFα). NGR-hTNF selectively binds to CD13-expressing blood vessels. CD13 is upregulated by tumour hypoxia/angiogenesis, which associate with high lactate dehydrogenase (LDH) serum levels. NGR015 enrolled patients with malignant pleural mesothelioma (MPM) who progressed on a first-line pemetrexed-based regimen; 200 patents were randomised to weekly NGR-hTNF and 200 patients were randomly assigned to placebo, both administered with best investigator choice, which included gemcitabine, vinorelbine or doxorubicin in 95% of patients or supportive care for 5% of patients. Patient reported outcome (PRO) was assessed by the malignant pleural mesothelioma-lung cancer symptom scale (MPM-LCSS) questionnaire, based on a 100-mm visual analogy scale (with 0 as best rating) for 5 major symptoms, including appetite loss, fatigue, cough, dyspnoea and pain, and 3 summary items of total distress, activity and quality of life (QoL). PRO measures were the time to symptomatic deterioration (TSD; ≥ 25% increase) and responder analysis (≥ 10% decrease). The trial also evaluated baseline LDH levels (median 274 U/L; IQR 196 to 388) as a predictor of outcome following treatment with NGR-hTNF.

The completion rate and scores for the PRO were balanced between treatment arms. The scores were found to inversely correlate with overall survival (OS; $p < 0.0001$). Analyses of the intent to treat population reveal that TSD (HR 1.01; $p = 0.97$) and OS (HR 0.94; $p = 0.61$) did not differ between arms. Predefined OS analyses indicated an interaction only between treatment and treatment-free interval (TFI) from end of first-line to start of second-line therapy (HR 0.54; $p = 0.008$). Patients having a short TFI, defined as less than the median 4.8 months (n=198) demonstrated improved OS and TSD with NGR-hTNF over placebo; median OS was 9.0 versus 6.3 months, HR 0.69 ($p = 0.02$) and median TSD was 3.3 versus 2.8 months, HR 0.66 for the respective treatments. With NGR-hTNF and best investigator choice, 49% compared to 37% of patients, respectively, showed a decrease in LDL levels of ≥ 10% was 49% versus 37%. The median OS in patients showing a lowered LDH level was 15.6 with NGR-hTNF versus 8.4 months with best investigator choice. Overall, LDH levels were inversely related to TFI ($p < 0.0001$) and LDH levels were higher in patients having short rather than long TFI ($p < 0.0001$). In the short TFI subset, the HR for PFS was 0.56 ($p = 0.001$) with LDH ≥ 1st quartile and 0.36 ($p = 0.001$) with LDH ≥ 3rd quartile and the increase in median OS was 3.7 and 7 months, respectively. NCT01098266. Gregorc *et al.* Abstract 1508PD

Practice point and future research opportunities

This study demonstrated that NGR-hTNF plus best investigator choice of treatment improved overall survival over best investigator choice in patients with malignant pleural mesothelioma

who progress rapidly after front-line therapy. Quality of life was comparable between the two groups. LDH levels seem to be a marker for NGR-hTNF activity.

Resection of stage III thymic epithelial tumours emerges as a significant prognostic factor for improved overall survival

Maria Virginia Bluthgen, Cancer Medicine, Institut Gustave Roussy, Villejuif, France, reviewed the RYTHMIC (Réseau tumeurs THYMiques et Cancer), a French nationwide network for thymic epithelial tumours (TET) to evaluate the treatment outcome following tumour board recommendations and a multidisciplinary approach. The investigators conducted a retrospective analysis of 150 cases of stage III TET discussed at the RYTHMIC tumour board from January 2012 to December 2015. Clinical, pathologic and surgical data were prospectively collected in a central database and survival rates were determined by Kaplan-Meier estimation.

The patients' median age was 64 years (range: 18 to 91 years), 56% of patients were male, 47% of patients had thymoma A-B2, and 47% of patients had B3-thymic carcinoma. Autoimmune disorder was also present in 12% of patients and 76% of these patients had myasthenia. Surgical treatment was the most often recommended modality and was given to 134 (90%) patients, which was followed by radiotherapy in 90 patients, and 26 patients received preoperative chemotherapy. The resection rate (R0) was 53%.

Of 38 patients determined not to be surgical candidates at diagnosis, 26 patients became resectable after induction chemotherapy and the R0 rate in this cohort was 58%. Patients who were not resected (n=12) received primary treatment with chemotherapy plus radiotherapy and/or chemotherapy. The recurrence rate in patients overall was 38% and the first sites of recurrence were pleural in 32 patients and lung in 12 patients. For all TET patients, the 5-year overall survival (OS) and disease-free survival (DFS) rates were 88% and 32%, respectively. On multivariate analysis, receiving surgery as the primary treatment modality emerged as the most significant prognostic factor for OS ($p < 0.001$) followed by histology ($p = 0.02$), and gender ($p = 0.04$). Prognostic factors for DFS were histology ($p=0.02$) and the administration of adjuvant radiotherapy ($p = 0.05$). Completeness of resection was not associated with survival in this cohort. Bluthgen *et al.* Abstract 1509PD

Practice point and future research opportunities

The heterogeneity of stage III thymic epithelial tumours makes determination of an optimal treatment approach difficult; this analysis used a national network of thymic epithelial tumours to determine that surgery was the treatment most often given to patients with stage III TET. Surgery followed by adjuvant radiotherapy improved outcome irrespective of the resection rate. Patients with stage III TET that were not surgical candidates at diagnosis who received induction chemotherapy to reduce the tumour followed by surgery showed an improved resection rate.

Pathological central review of 400 thymic epithelial tumours highlights the value of the RYTHMIC French national network

Lead author Thierry Molina, Department of Pathology, GH Necker - Enfants Malades, Paris, France, and colleagues performed this audit of discordance between the diagnosis made by the initial institution and the panel review of RYTHMIC (Réseau tumeurs THYMiques et Cancer), a nationwide network for thymic epithelial tumours (TET) initiated in 2012 by the French National Cancer Institute. The network goal is the management of a clinical tumour board and central pathologic review of all cases based on initial histopathological diagnosis.

Pathological central review of patients diagnosed with TET from January 2012 to May 2016 was made by a panel of 10 expert pathologists from the working group of RYTHMIC. Assessment of diagnostic agreement was made according the WHO 2004/2015 and new International Thymic Malignancy Interest Group (ITMIG) proposals for histologic typing and staging. Discordances were classified as “major” when they would have changed the therapy or management of patients according to the RYTHMIC guidelines.

Review of 400 specimens that was made according to histological subtype and/or staging revealed 172 discordances in 157 (39%) patients; of these, 111 concerned histological diagnosis and 61 discordances regarded the tumour stage. A total of 31 major treatment altering discordances were identified in 29 (7%) patients that would have changed the post-surgical treatment recommendation concerning adjuvant radiotherapy for 18 patients and the management of disease should have been modified for 11 patients.

The most frequently occurring disagreement between the initial and RYTHMIC network was the sub-diagnosis of stage III disease, which emphasised the underlying difficulty in defining pericardial and/or mediastinal pleura histological invasion. Also, major disagreement between the initial and panel pathology’s stage and subsequent interpretation by the working group at the national tumour board was found in 4 patients, underscoring the importance of having an expert pathologist on the RYTHMIC network committee. Molina *et al.* Abstract 1510PD

Practice point and future research opportunities

This study adds to the growing body of evidence that emphasises the importance of tumour boards and registries and the value that central review by experts provides to patient care. The RYTHMIC experience confirms the relevance of an expert histopathological panel diagnosis of thymic malignancies for better decision-making, particularly concerning post-operative radiotherapy to avoid over- or under-treatment of the patients.

TRANSLATIONAL RESEARCH

Tumour gene expression used to direct clinical decision-making for patients with advanced cancers

Janessa Laskin, Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, headed a team of Canadian investigators in evaluating the integration of whole genome sequencing, including DNA and RNA expression information, into oncology practice in the Personalized OncoGenomics (POG) study. Between July 2012 and April 2016, patients were enrolled with advanced tumours and minimum survival of 6 months. All patients provided a tumour biopsy and blood sample for comprehensive DNA (80X) and RNA sequencing followed by bioinformatic analysis including assembly, annotation, and mining of the data to identify potentially targetable somatic aberrations, gene expression changes, or other putative cancer "drivers". RNA expression information from tumour RNA sequencing was also compared to the TCGA and Illumina body map. The results obtained from sequencing patient tumours were assessed in a multidisciplinary Clinical Genomics Tumour board and categorised the results for clinical actionability as informative, actionable or neither.

Complete sequencing data were available for 217 patients. The vast majority, 165 patients, had clinically actionable results and no actionable pathway could be identified in just 52 patients. No samples were found to be informative only. The information from the 165 actionable patients was used to provide personalised therapy directed by POG data for 71 patients and POG directed therapy could be offered upon progression to 34 patients. POG directed therapy was not administered to 60 patients; 24 due to poor performance status or death, and 16 did not receive POG directed therapy because no clinical trial or off-label treatment was available. In 20 patients, the POG data was not utilised. Of the 71 patients having POG directed treatment, 13 received this treatment within a clinical trial, 29 patients received off label treatment, and 29 patients received treatment within guidelines of disease site. RNA information was used in 40% of treatment decisions, 45% of treatment decisions were based on a combination of DNA and RNA information, and 15% of treatment decisions were based on solely on DNA information. NCT02155621. Laskin *et al.* Abstract 1519O

Practice point and future research opportunities

This study demonstrated that sequencing information from patients' tumours can provide information on targetable DNA or RNA aberrations to be directly translated into clinical treatment decisions. The whole genome analyses used here have the potential to identify the full landscape of genomic abnormalities within cancers, and can therefore be used to provide rationales for cancer treatments. This analysis evaluated how physicians used the data for clinical decisions and the role of RNA data in identifying actionable targets. Data from DNA abnormalities alone corresponds to the rate noted in historical panel-associated drug matching trials; however, the availability of RNA expression information or both DNA/RNA information greatly increased the ability to identify clinically actionable targets. With the support of the multidisciplinary tumour

board and a tiered data system, oncologists had sufficient confidence in the results to seek clinical trials and off-label therapies based on genomic data in the majority of patients.

Lurbinectedin is active in PARP-inhibitor resistant germline BRCA patient derived xenographs and cisplatin efficacy is unaffected by lurbinectedin resistance

Cristina Cruz, Medical Oncology, Hospital Vall d'Hebron and Vall d'Hebron Institute of Oncology, Barcelona, Spain and colleagues used 10 patient-derived xenographs (PDXs) obtained from lurbinectedin-naive patients who had germline BRCA mutations (gBRCA) to characterise resistance to PARP inhibitors and the mechanism of this resistance, including its effect on lurbinectedin. The investigators evaluated the antitumor activity of lurbinectedin at 0.18mg/kg i.v. plus cisplatin at 6 mg/kg i.v. every 7 days for 5 cycles in the previously lurbinectedin-naïve patients. Of the 10 patient samples, 8 showed resistance to PARP inhibitors and 2 were PARP inhibitor-sensitive; additionally, the combination was tested on one additional PDX implanted at time of progression on lurbinectedin. Exome sequencing analysis was done in 5 paired tumour biopsies taken pre- and post-lurbinectedin treatment.

The results suggest that the mechanisms of resistance to PARP inhibitors does not confer resistance to lurbinectedin. Lurbinectedin was active and showed antitumour activity, consisting of partial response, complete response or stabilisation in 6 (75%) of the 8 PDXs that were resistant to PARP inhibitors. Exome sequencing of gBRCA tumours that were resistant to lurbinectedin resistant tumours revealed the acquisition of genetic alterations in 5 samples that could disrupt the nucleotide excision repair (NER) pathway, which may impair sensitivity to PM01183. These same alterations confer sensitivity to cisplatin in vitro and in vivo. The PDX model implanted at progression on lurbinectedin demonstrated lurbinectedin resistance but remained sensitive to cisplatin, suggesting that the NER alterations putatively driving resistance to lurbinectedin do not compromise cisplatin efficacy. Cruz *et al.* Abstract 1520O

Practice point and future research opportunities

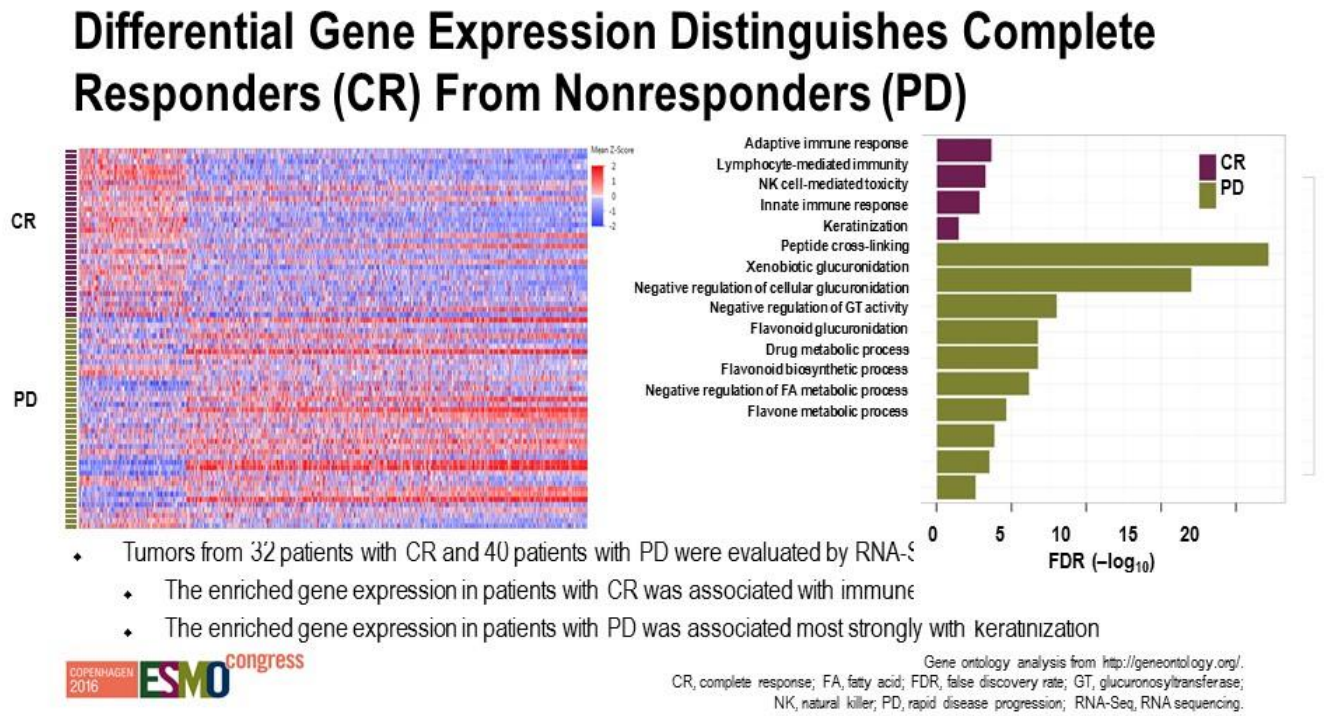
Lurbinectedin is a trabectedin analogue that inhibits transactivated transcription and induces DNA double-strand breaks that has demonstrated remarkable clinical activity in patients with germline BRCA-related metastatic breast cancer. Previous studies also demonstrated lurbinectedin activity in patients resistant to platinum-based chemotherapy. This study assessed the activity of lurbinectedin and the mechanisms of primary and acquired resistance to lurbinectedin and the potential impact on the efficacy of PARP inhibitors or platinum salts.

These findings suggest that lurbinectedin is active in the presence of resistance of PARP inhibitors and that primary or developed resistance to lurbinectedin does not compromise platinum efficacy. This knowledge may aid in determining the optimal therapeutic sequence to maximise the clinical benefit in the metastatic breast cancer setting.

Baseline immune factors differ between responding and non-responding patients with BRAFV600-mutated melanoma

Lead investigator Antoni Ribas, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles, CA, USA, explained that patient responses to the BRAF inhibitor, vemurafenib, and the MEK inhibitor cobimetinib vary, although both sole vemurafenib and vemurafenib plus cobimetinib have demonstrated improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) in patients with BRAFV600-mutated metastatic melanoma.

Together with colleagues, Dr. Yibing Yan, Oncology Biomarker Development, Genentech, Inc., South San Francisco, USA, and Dr. Ribas conducted this study to identify the baseline genetic features in responding and non-responding patients to determine the role they play in response to these agents. This study compared genomic features of tumours at baseline with respect to patients achieving complete response (CR) versus those showing progressive disease (PD) in response to treatment. Tumour samples taken prior to treatment in the BRIM2, BRIM3, BRIM7, and coBRIM trials from patients showing CR or PD at the first evaluation were analysed by whole exome sequencing (WES) and RNA sequencing. The differences in gene signatures between patients having CR and PD were tested by ANOVA and represent the mean Z-score of all components. Associations of gene expression with PFS or OS were assessed by Cox proportional hazards modelling.



Differential gene expression distinguishes complete responders from non-responders.

WES was performed on baseline melanoma samples from 52 patients having CR, and 78 patients showing PD following treatment with cobimetinib combined with vemurafenib or sole vemurafenib.

Analysis of the genomic features of biopsies of patients with metastatic BRAFV600-mutated melanoma revealed that tumour samples taken at baseline from patients who went on to achieve CR showed higher expression of pre-existing tumour immunity features than patients who experienced PD at the first evaluation.

Although the overall mutational load was not significantly different in samples from both groups, samples from patients with PD showed higher rates of MITF amplification and TP53 mutation than patients with CR; the respective rates were of MITF amplification were 18% versus 4% and TP53 mutation rates were 19% versus 5% in patients with PD and CR, respectively. The profile of patients with CR more commonly included NF1 deletion and deleterious mutations at 12% versus 3% in PD.

Gene expression was analysed with RNA sequencing on tumours from 32 CR and 40 PD revealed differential expression of 415 genes between patient cohorts that were also associated with PFS or OS. The investigators found that gene expression profiles in tumours of patients with CR were over-represented with adaptive and innate immune responses, such as gene signatures of CD8 T effector cells, cytolytic T-cells, antigen presentation and NK cells.

Previously, Dr. Ribas and colleagues identified common features of melanoma that showed innate resistance to anti-PD1 immune therapy, defined as innate anti-PD1 resistance signatures (IPRES; Hugo et al. Cell. 2016;165:35-44). In this analysis of resistance to BRAF/MEK inhibition, the authors found it interesting that there were higher levels of gene expression of 19 keratin and 7 kallikrein genes in tumours from patients having PD tumours and remarked that this was reminiscent of the “keratin” subtype of tumour proposed by The Cancer Genome Atlas (TCGA) project. Ribas *et al.* 1111O

Practice point and future research opportunities

These exploratory analyses revealed baseline genomic differences between melanoma from patients showing CR compared to those having PD after treatment with cobimetinib combined with vemurafenib or vemurafenib alone. Overall, melanomas from patients achieving CR with either regimen had higher levels of pre-existing tumour immunity features, whereas melanoma samples from patients showing PD predominately display the “keratin” molecular subtype. This finding calls for further investigation of interaction of all significantly enriched molecules.

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Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

Acknowledgment

ESMO would like to thank you Virginia Powers, PhD for editorial assistance in preparation of this report.

ESMO would like to thank you Drs Judith Balmaña, Mark Andrew Glaire, Pierre Laurent-Puig, Sara Pusceddu, Antoni Ribas, Phillipe Rochigneux, Alexa Schrock and Yibing Yan for giving their permission to publish the images from the studies presented during the ESMO 2016 Congress in the ESMO Scientific report.

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