oncology PRO®
Educational Portal for Oncologists

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO 2018 Congress

19-23 October 2018

Munich, Germany

Table of Contents

Summary

The European Society for Medical Oncology (ESMO) 2018 Congress was held from 19 to 23 October in Munich, Germany. Once again ESMO 2018 proved to be the leading international oncology event in Europe, bringing together stakeholders from around the world who are committed to providing optimal cancer care to patients.

Of the record-breaking 3352 abstracts submitted, 2052 were accepted, of which 66 were late-breaking abstracts. In all, data from 747 clinical trials were presented representing 115'986 patients, from those 82,492 treated in randomised clinical trials. Among clinical studies, 123 were phase I, 236 phase I/II, 235 phase II, 7 phase II/III, and 146 phase were phase III clinical trials. The abstracts represented cutting edge research and delineated the most current treatment strategies.

Numerous presentations were accompanied with simultaneous publications in the prestigious journals such as *The New England Journal of Medicine*, *The Lancet*, *The Lancet Oncology*, *Journal of Clinical Oncology* and *Annals of Oncology*.

ESMO 2018 provided a forum for the increasing number of trials testing immunotherapy in the first-line setting, strategies for (neo)adjuvant treatment in many cancer types, as well as combination treatments with other treatment modalities, and plasma-based assays for monitoring mutations over the course of disease progression.

A brief summary of these trials as well as the many diverse findings in myriad topics presented at the ESMO 2018 Congress follows.

INTRODUCTION

The European Society for Medical Oncology (ESMO) 2018 Congress was held from 19 to 23 October in Munich, Germany. Once again ESMO 2018 proved to be the leading international oncology event in Europe, bringing together stakeholders from around the world who are committed to providing optimal cancer care to patients.

ESMO 2018 also hosted the annual congress of the European Oncology Nurses Society, EONS11. The EONS11 three-day nursing tract focused on education and discussion of the latest developments in cancer nursing, such as cancer nursing leadership, symptom management, patient safety, and new cancer research as well as techniques to improve patient outcomes through doctor-nurse collaboration.

Attendance at the 2018 ESMO congress was increased by 16.8% over the 2017 congress in Madrid, breaking all previous attendance records. ESMO 2018 welcomed 27'940 attendees who travelled from 137 countries to network and to discuss the latest developments in cancer research and patient care. The largest percent (13.98%) of participants came from United States of America, followed by Germany (9.9%), France (6.8%), the United Kingdom (6.50%), China (5.98%), Switzerland (4.11%), Italy (4,08%), Spain (3,9%), Japan (3,24%), and Belgium (2,09%).

In all, 57.70% of delegates travelled from Europe, 15.33% from North America, 14.12% from Asia, 5.31% of delegates came from Central and South America, 4.86% the Middle East, 1.59% from Africa, and 1.09% of delegates travelled from Australia and the Pacific which bears testimony to the international nature of this congress.

Most (84.72%) of congress participants were delegates with the remainder comprised of exhibitors/industry and press. Although the majority, 57.82% of delegates, were medical oncologists, the delegate population comprised many diverse backgrounds, including 7.92% of clinical oncologists, 6.18% haemato-oncologists, 3.20% industry medical staff, 2.31% pneumologists or chest physicians, 2.27% radiation oncologists, 2.07% basic researchers or scientists, and 2.05% of the delegates providing information at registration were oncology nurses, with the remainder made up by surgical oncologists, haematologists, patient advocates, oncology pharmacists, paediatric oncologists, immunologists, as well as many other medical professionals.

This occupational diversity was reflected in the range of professional interests expressed by the congress participants, which covered the spectrum of oncology from basic science to palliative care. A total of 64.38% of attendees indicated that breast cancer was their primary interest, followed by gastrointestinal malignancies (58.95%), genitourinary cancers (45.23%), chest malignancies (42,58%), and gynaecological malignancies (39.81%). Most delegates (64.10%) expressed an interest in learning about anti-cancer agents followed by immunotherapy and/or tumour immunology (62.67%). Clinical research was cited by 46.95% of respondents as their primary topic of interest, biological therapy by 42.86% of respondents, and 36.19% of delegates said personalised cancer medicine was the topic

they came to ESMO 2018 to explore. The respondents answered that they were drawn to ESMO 2018 by the high-quality educational programme, the presentation of new data, and the networking-friendly environment.

Most congress participants agreed that ESMO 2018 would enable them to deliver a better standard of care to their patients and also helped to generate new research ideas. The education offered at the congress was rated as very good, bordering on excellent. The respondents stated that the information presented was well balanced and supported by adequate evidence, as well as being useful and relevant to their research and/or practice. The majority of respondents stated that the congress offered updates on the latest breakthroughs in translational and clinical cancer research that enabled the understanding of the clinical perspective of scientific advances in cancer biology, diagnostics, and new treatment approaches.

These high marks were the result of a comprehensive scientific programme that was formulated by oncology experts to ensure widespread multidisciplinary and multi-professional appeal. The scientific programme captured the diverse aspects of oncology in educational symposia and state of the art teaching lectures.

Of the record-breaking 3352 abstracts submitted, 2052 were accepted, of which 66 were late-breaking abstracts. In all, data from 747 clinical trials were presented representing 115'986 patients, from those 82,492 treated in randomised clinical trials. Among clinical studies, 123 were phase I, 236 phase I/II, 235 phase II, 7 phase II/III, and 146 phase were phase III clinical trials. The abstracts represented cutting edge research and delineated the most current treatment strategies, primarily focusing on the topics of gastrointestinal cancer, both colorectal (304) and non-colorectal (254), followed by metastatic non-small cell lung cancer (241), biomarker research (234), gynaecological cancers (169), and immunotherapy (168). The oral and poster discussion sessions featured faculty that placed abstract findings into clinical perspective and discussed how the results may impact the current standard of care. In addition, the input from invited discussants and a well-informed audience in the proffered paper sessions provided lively discussion. Many (5.9%) abstracts were chosen for oral presentation and 10.5% for poster discussion, with the remainder of abstracts presented as posters. Numerous presentations were accompanied with simultaneous publications in the prestigious journals such as *The New England Journal of Medicine*, *The Lancet*, *The Lancet Oncology*, *Journal of Clinical Oncology* and *Annals of Oncology*.

ESMO 2018 provided a forum for the increasing number of trials testing immunotherapy in the first-line setting, strategies for (neo)adjuvant treatment in many cancer types, as well as combination treatments with other treatment modalities, and plasma-based assays for monitoring mutations over the course of disease progression.

A brief summary of these trials as well as the many diverse findings in myriad topics presented at the ESMO 2018 Congress follows.

BASIC SCIENCE

Deep sequencing of sequential patient samples identifies lethal subclones that act as genetic drivers of tumour evolution in metastatic NSCLC

Mariam Jamal-Hanjani of the University College London Cancer Institute, Cancer Research UK Lung Cancer Centre of Excellence in London, UK presented data from the preliminary analysis done on the first 4 patients analysed in the Posthumous Evaluation of Advanced Cancer Environment (PEACE) study, which is investigating the genetic and phenotypic relationships between primary and metastatic tumours. Dr. Jamal-Hanjani and colleagues used a cohort of patients enrolled in the TRACERx study, which tracks tumour evolution from primary to relapsed disease in non-small cell lung cancer (NSCLC). The investigators performed multiregional sampling of primary tumours at surgical resection, and metastatic tumours in the post-mortem setting. DNA was extracted from fresh frozen tissue and deep whole-exome sequencing (WES) was done and analysed using bioinformatic tools developed to assess tumour clonal architecture and evolutionary pathways.[1] PEACE has recruited over 100 patients and captured over 50 tissue harvests to date. The investigators are working towards establishing a model for tumour progression and the metastatic process, as well as identifying the potential mechanisms that are involved in tumour evolution and the development of therapeutic resistance.

This evaluation demonstrated the presence of driver events, including mutations and somatic copy number aberrations, in both early and late evolution, as well as continued tumour diversification that further drives genome instability. The researchers also uncovered different patterns of metastatic seeding using evolutionary phylogenetic analyses, and were able to demonstrate the timing of cancer events from primary to metastatic disease. Dr. Jamal-Hanjani pointed out that data arising from PEACE have already demonstrated implications for tracking disease progression.[2] PEACE data have also informed the emergence of drug resistance and the identification of distinct patterns of metastatic spread with potential prognostic implications.[3] NCT03004755. Jamal-Hanjani *et al.* Abstract LBA11

Practice point and future research opportunities

PEACE is a unique study leveraging the true longitudinal sampling from diagnosis to death that has the potential to inform understanding of the metastatic process, and to reveal the lethal subclone(s) that are involved in branched tumour evolution. WES data from primary and metastatic tumours in the cohort of patients recruited into both TRACERx and PEACE can help decipher the clonal dynamics and evolutionary trajectory of lung cancer.

Citations:

1. Jamal-Hanjani M, Wilson GA, McGranahan N, *et al*. Tracking the Evolution of Non-Small-Cell Lung Cancer. *N Engl J Med* 2017; 376(22):2109-2121.

2. Abbosh C, Birkbak NJ, Wilson GA, *et al*. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature* 2017; 545(7655):446-451.

3. Turajlic S, Xu H, Litchfield K, *et al*. Tracking Cancer Evolution Reveals Constrained Routes to Metastases: TRACERx Renal. *Cell* 2018; 173(3):581–594.e12.

Homology-directed repair-defective lung adenocarcinomas detected in circulating tumour DNA

Niki Karachaliou, Institute of Oncology Rosell, University Hospital Sagrat Cor, Grupo QuironSalud, Barcelona, Spain, presented results on behalf of the Spanish Lung Liquid versus Invasive biopsy Program (SLLIP), which sought to identify whether homology-directed repair (HDR) mutations and alterations were present in samples of patients with advanced lung adenocarcinoma. The rationale was that tumours lacking key HDR regulators, such as, *BRCA1, BRCA2*, and AT-rich interaction domain 1A (*ARID1A*) are hypersensitive to PARP inhibitors and mutations in HDR have also been demonstrated response to PD-1 or PD-L1 blockade. A secondary aim of the study was to identify additional drivers and actionable mutations, particularly in the absence of *EGFR, KRAS, ALK* and *ROS* alterations. The investigators used the 73-gene ctDNA Guardant 360 assay that had been validated by the SLLIP group (NCT03248089) for the detection of targetable activating alterations in lung adenocarcinoma. Determination of deleterious mutation status was based on ClinVar and BRCA Exchange databases, as well as expert curation.

From August 2016 to June 2017, genomic profiling was performed using plasma obtained from 185 treatment-naïve patients with advanced lung adenocarcinoma. The patients had a median age of 66 years, 64% were male, and 81% of patients were smokers or ex-smokers. Most SLIPP patients had received first-line platinum-based chemotherapy. Any genomic alteration in DNA damage responsive (DDR) genes and ARID1A were identified in 25.4% of patient samples; including 12 *BRCA1*, 13 *BRCA2*, 4 *ATM*, 2 *MLH1*, and 24 *ARID1A* alterations. More than 90% of the variants in *BRCA1, BRCA2*, and *MLH1* were of unknown significance or likely benign. The 12 *BRCA1*-mutant positive patients had a median of 3 (range, 1 to 15) co-occurring genetic alterations. One patient had an *EGFR* mutation, and 4 had *KRAS* mutations. In the 13 *BRCA2*-mutant patients, a median 4 (range, 1 to 14) co-occurring genetic alterations were detected, including one *EGFR* mutation, one *MET* exon 14, and 4 *KRAS* mutations. Three of 4 *ATM*-mutant patients had co-occurring *EGFR* or *KRAS* alterations; 3 of the *ATM* mutations were likely pathogenic, according to the investigators. The 2 patients with *MLH1* mutations had co-occurring *KRAS* alterations. In the 24 patients with *ARID1A*-mutations, a median of 4 (range, 1 to 15) co-occurring genetic alterations were identified that included 6 patients with *EGFR* and 8 with *KRAS* mutations. More than half of the *ARID1A* alterations were loss-of-function mutations. NCT03248089. Karachaliou *et al.* Abstract 1895PD

Practice point and future research opportunities

This is the first report of the detection of *ARID1A* mutations in patients with lung adenocarcinoma. *ARID1A* is one of the genes with the highest mutation rate across several types of tumours. Evaluation of the ctDNA of patients with lung adenocarcinoma could identify HDR mutations that could be sensitive to treatment with PARP inhibitors and PD-1/PD-L1 blockade.

Mutational landscape of metastatic cancers defined by using prospective tumour sequencing in a community practice cancer programme

Ricardo H. Alvarez, Medical Oncology, Cancer Treatment Centres of America in Newnan, USA headed a research team in conducting large-scale comprehensive genomic profiling (CGP) from January 2013 to September 2017 in order to match patients to treatment. The investigators performed CGP using hybrid-capture next generation sequencing (NGS)-based CGP assays; 3 genomic platforms were utilised: Foundation One comprising 315 genes was used for 89% of tests, FoundationOne-Heme with 405 genes in 6%, and FoundationAct, comprising 62 genes, was used in 5% of patient testing. This analysis included samples obtained from 6,177 patients with advanced cancer over the course of clinical care in the setting of a community practice cancer network for the purpose of making therapy decisions. The median age of the patients was 56 (range, 18 to 94) years, 61% of patients were female, and 68% were Caucasian. The most common tumour types studied were breast (18%), colorectal (15%), lung (14%), gynaecological (11%), and unknown cancer (10%).

A total of 6496 CGP assays were performed, with genomic alterations (GAs) identified in 5839 (94%) samples; the most often detected GAs were amplification in 32% of cases. GAs classified as clinically relevant were identified in 47.0%, and not clinically relevant GAs were found in 52.6% of samples. The most frequently detected clinically relevant GAs were in *KRAS* in 23%, and *PIK3CA*, which was detected in 15% of cases.

Review of the treatment history of 4490 patients indicated that 1169 (23%) patients were ordered a genomically-matched treatment. Of these, 662 (57%) patients were provided an FDA approved agent in a different tumour type, and 178 (15%) patients were referred to a matched mechanism driven clinical trial. Future analysis will explore outcomes for this subset of patients. The frequency of matched treatment in clinical trials increased from 2013 to 2017 as access to the Targeted Agent and Profiling Utilization Registry (TAPUR). Alvarez *et al.* Abstract 1891O

Practice point and future research opportunities

This study demonstrates that large-scale prospective tumour profiling can be successfully carried out and provides the detection of GAs that can be therapeutically targeted. This large series of patients with diverse tumours were assayed with CGP, which identified 23% of

patients who could benefit from matched treatment, which was predominantly targeted therapy. The increasing frequency of matching treatment over time and the advent of immunotherapy and matching with PD-L1 and tumour mutational burden may further increase the proportion of this population.

BIOMARKERS

Plasma cell-free DNA assay for early multi-cancer detection shows good sensitivity

The Circulating Cell-Free Genome Atlas (CCGA) study is a prospective, multicentre, observational study that aims to develop a plasma cell-free DNA (cfDNA)-based multi-cancer detection assay, explained Minetta C. Liu, Division of Medical Oncology, Department of Oncology, Mayo Clinic Cancer Centre in Rochester, USA. This type of non-invasive cfDNA blood test could detect multiple cancers at early stages when treatment is more likely to be effective and possibly decrease cancer mortality. The research team collected 2402 clinically evaluable samples from non-cancer controls and patients with newly diagnosed untreated cancer comprising 20 tumour types representing all disease stages. The samples were categorised into a training set that included 580 controls and 878 patients and a test set with 368 controls and 576 patients. The controls and patients were well matched and had similar age, smoking status, and gender. Both sets were analysed as a preplanned substudy using prototype sequencing assays, which included paired cfDNA/white blood cell (WBC, 60000X) targeted sequencing, paired cfDNA/WBC whole genome sequencing (30X), cfDNA whole genome bisulfite sequencing (WGBS, 30X). Sensitivity was estimated at 98% specificity.

Cancers occurring in more than 5 patients in the training and test sets were reported. Of the 3 assays, the WGBS assay returned the highest sensitivity and the results were also consistent across the targeted, WGS, and WBC assays. A WBC signal was used to correct for clonal haematopoiesis. Stage I-IV cancer detection was consistent in training and test sets. The training set analysis revealed cancer-specific sensitivities (high-signal cancers) ranging from 54% to 92%. The individual cancers detected in the test set included 22 hormone receptor negative breast (sensitivity 36%; 95% confidence interval [CI], 17-59), 45 colorectal (sensitivity 60%; 95% CI, 44-74), 7 oesophageal (sensitivity 43%; 95% CI, 10-82), 12 head and neck (sensitivity 50%; 95% CI, 21-79), 15 hepatobiliary (sensitivity 73%; 95% CI, 45-92), 47 lung (sensitivity 70%; 95% CI, 55-83), 22 lymphoma (sensitivity 64%; 95% CI, 41-83), 7 ovarian (sensitivity 71%; 95% CI, 2 9-96), and 23 pancreatic (sensitivity 74%; 95% CI, 52-90). Results were also consistent between training and test sets regarding stage I-III and stage IV cancers. Further assay and clinical development of a multi-cancer cfDNA test in large-scale clinical studies, including CCGA, is ongoing. NCT02889978. Lui *et al.* Abstract 50O

Practice point and future research opportunities

This study showed that a non-invasive, cfDNA-based blood test was able to detect multiple cancers at various stages, with results that were consistent in the training and test sets. This is a promising approach to be used in multi-cancer early detection, including high mortality unscreened cancers where early treatment can impact mortality.

BREAST CANCER

Atezolizumab added to nab-paclitaxel improves survival in treatment-naive, locally advanced or metastatic triple-negative breast cancer

Lead author Peter Schmid, Centre for Experimental Cancer Medicine, Barts Cancer Institute, London, UK presented the final progression-free survival (PFS) and first interim overall survival (OS) findings from the phase III, double blind, randomised IMpassion130 trial, which evaluated the efficacy and safety of PD-L1 inhibition with atezolizumab plus nab-paclitaxel versus placebo/nab-paclitaxel in treatment-naïve patients with metastatic triple-negative breast cancer (TNBC). Patients with histologically documented, metastatic TNBC were randomly assigned 1:1 to receive nab-paclitaxel at 100 mg/m^2 intravenously on days 1, 8, and 15 of the 28-day cycle plus atezolizumab at 840 mg intravenously (n = 451) on days 1 and 15 of a 28-day cycle and 451 patients received the same regimen of nab-paclitaxel plus placebo. Treatment was given until disease progression or unacceptable toxicity. The patients' median age was 55 and 56 years, 57% and 60% had ECOG performance status 0 in the respective cohorts, and 63% of patients in both arms had prior neoadjuvant treatment. The co-primary endpoints were PFS and OS in both the intent-to-treat (ITT) and PD-L1–positive populations; secondary endpoints included overall response rate (ORR), duration of response (DoR), and safety. Patients were stratified by prior taxane use, liver metastases, and PD-L1 expression, with PD-L1 positivity defined as at least 1% on tumour-infiltrating immune cells.

After median follow-up of 12.9 months, the median PFS in the ITT population was 7.2 months (95% confidence interval [CI], 5.6-7.5) with atezolizumab/nab-paclitaxel and 5.5 months (95% CI, 5.3-5.6) with nab-paclitaxel (hazard ratio [HR] 0.80; 95% CI, 0.69-0.92; p = 0.0025). One-year PFS rates were 24% (95% CI, 20%-28%) versus 18% (95% CI, 14%-21%) in the atezolizumab combination versus nab-paclitaxel arms, respectively. In this population, median OS was 21.3 (95% CI, 17.3-23.4) months versus 17.6 (95% CI, 15.9-20.0) months (HR 0.84; 95% CI, 0.69 -1.02; p = 0.084).

However, atezolizumab benefit was more pronounced in the PD-L1–positive population where patients demonstrated a clinically meaningful median PFS of 7.5 months (95% CI, 6.7-9.2) with atezolizumab/nab-paclitaxel and 5.0 months (95% CI, 3.8-5.6) with nab-paclitaxel (HR 0.62; 95% CI, 0.49-0.78; p < 0.0001). The one-year PFS rates were 29% (95% CI, 22%-36%) with atezolizumab/paclitaxel and 16% (95% CI, 11%-22%) with nab-paclitaxel. The interim analysis of the PD-L1–positive population also showed a clinically meaningful improvement in OS with atezolizumab of 25.0 months versus 15.5 months with nab-paclitaxel (HR 0.62; 95% CI, 0.45-0.86). The OS rates at 2 years were 54% and 37% in the respective treatment arms.

Regarding secondary endpoints, the ORR in the ITT population was 56% versus 46% with atezolizumab versus paclitaxel (p = 0.0021) and ORR in the PD-L1 subset was 59% versus

43%, respectively (p = 0.0016). Median DoR with the respective treatments was 7.4 months versus 5.6 months in the ITT population and 8.5 versus 5.5 months in the PD-L1 subgroup.

The incidence of all-grade adverse events (AEs) was similar (99% versus 98%) between arms. The grade 3/4 AEs occurred in 49% of patients with atezolizumab/nab-paclitaxel and in 42% of patients on nab-paclitaxel. NCT02425891. Schmid *et al.* Published simultaneously in the *NEJM*.[1] Abstract LBA1_PR

Practice point and future research opportunities

This is the first time that improved survival has been demonstrated by immunotherapy in a phase III trial in metastatic TNBC, which may be practice-changing in the treatment of TNBC. These results suggest first-line atezolizumab plus nab-paclitaxel may be a therapeutic option in metastatic TNBC, which accounts for 15% of breast cancers. The benefit with the combination was optimal in patients having expression of PD-L1, which is mainly expressed on tumour-infiltrating lymphocytes in TNBC. The addition of atezolizumab to nab-paclitaxel reduced the risk of progression or death by 38% compared with nab-paclitaxel alone.

Citation

1. Schmid P, Adams S, Rugo H, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. NEJM 2018; 2018; 379:2108-2121.

2. Palbociclib improves overall survival in women with HR-positive, HER2-negative advanced breast cancer

Massimo Cristofanilli, Robert H. Lurie Comprehensive Cancer Centre of Northwestern University, Feinberg School of Medicine in Chicago, USA presented results of the final analysis of data from the PALOMA-3 trial on behalf of an international team of investigators. PALOMA-3 was a prospective, randomised phase III trial evaluating palbociclib, a first-in-class CDK 4/6 inhibitor, combined with fulvestrant in 521 women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer that had relapsed or progressed on hormonal therapy. Resistance to hormonal therapies develops over time in most patients with HR-positive breast cancer and inhibiting CDK4/6 has been identified as a target for overcoming or delaying the resistance. The women were randomly assigned to oral palbociclib at 125 mg per day plus fulvestrant at 500 mg according to current standard of care or placebo plus fulvestrant. The primary endpoint of the trial was progression-free survival (PFS) and overall survival (OS) was a key secondary endpoint.

The OS analysis was performed after a median follow-up of 44.8 months after 310 (approximately 60%) patients in the study had died. The OS was prolonged by 6.9 months with palbociclib plus fulvestrant; median OS was 34.9 months (95% confidence interval [CI], 28.8-40.0) compared to 28.0 months (95% CI, 23.6-34.6) with placebo plus fulvestrant. The OS was even more prolonged in 410 patients who had received prior endocrine therapy and

were endocrine sensitive, where the improvement in OS with palbociclib was 10.0 months longer than with fulvestrant; median OS was 39.7 months versus 29.7 months (hazard ratio [HR] 0.72; 95% CI 0.55–0.94), respectively. The OS was also significantly prolonged by 11.5 months in 210 patients without visceral disease; median OS in this cohort was 46.9 versus 35.4 months (HR 0.69; 95% CI 0.46–1.04), respectively. It should be noted that OS was the same with palbociclib plus fulvestrant and placebo plus fulvestrant in the subgroup of 108 women who were pre- or peri-menopausal at study entry; in these cohorts, median OS was 38.0 months (HR 1.07; 95% CI, 0.61-1.86).

According to Professor Cristofanilli, the OS data were in agreement with previously reported PFS results from PALOMA-3 wherein palbociclib plus fulvestrant showed significantly improved PFS of 11.2 compared to 4.6 months with fulvestrant, demonstrating an absolute difference of 6.6 months between treatments (HR 0.50; 95% CI, 0.40–0.62; $p < 0.000001$).

No new safety signals were observed with longer follow-up.

The PENELOPE-B and PALLAS randomised adjuvant trials of palbociclib in early stage breast cancer are ongoing. NCT01942135. Cristofanilli *et al.* Published simultaneously in the *NEJM*.[2] Abstract LBA2_PR

Practice point and future research opportunities

These findings from a pre-planned analysis of the PALOMA-3 phase III study represent the first-ever OS results for a CDK4/6 inhibitor in ER-positive/HER2-negative breast cancer. These data were much awaited, as the clinical benefit obtained with CDK4/6 inhibitors was incontestable, but the question remained whether the PFS benefit would translate into OS benefit. The limited OS data that was reported in other trials are now supported by the PALOMA-3 results, which strongly suggest that this treatment should become widely available for women with advanced HR-positive/HER2-negative disease. However, the study was unpowered for OS, so the data should be cautiously interpreted. Although the results strongly suggest that the PFS benefit may translate into OS benefit, the other trials conducted with CDK4/6 inhibitors will contribute to confirm the estimate of the OS benefit observed in this study.

Citations:

1. Cristofanilli M, Turner NC, Bondarenko I, *et al*. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncology* 2016; 17:425-439.

2. Turner NC, Slamon DJ, Ro J, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. NEJM 2018; 379:1926-1936.

Combined alpelisib and fulvestrant improve PFS in patients with advanced breast cancer and PIK3CA mutations

Fabrice André, the Institut Gustave Roussy, Villejuif, France presented findings on behalf of colleagues from the phase III randomised, double-blind SOLAR-1 trial investigating the efficacy and safety of alpelisib in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. Alpelisib targets phosphatidylinositol-3-kinase (PI3K), which is hyperactivated due to PIK3CA mutations that are present in approximately 40% of patients with HR-positive, HER2-negative advanced breast cancer. The rationale for the SOLAR-1 trial was provided by phase I trial results showing promising preliminary efficacy with alpelisib together with a manageable safety profile.[1] The SOLAR-1 trial randomised 572 postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer to receive oral alpelisib at 300 mg per day or placebo; both groups also received fulvestrant at 500 mg on days 1 and 15 of the initial treatment cycle and every 28 days thereafter. The patients had ECOG performance status ≤1 and had received one or more prior lines of hormonal therapy, but no chemotherapy, for advanced breast cancer. They had not previously received fulvestrant, or any PI3K, Akt or mTOR inhibitor, and were not on concurrent anti-cancer therapy. Testing of tumour tissue revealed PIK3CA mutations in 341 patients. The primary endpoint of SOLAR-1 was locally assessed progression-free survival (PFS) in patients with PIK3CA mutations.

At a median follow-up of 20.0 months, patients with PIK3CA mutations receiving alpelisib/fulvestrant demonstrated PFS that was almost twice as long as that observed in the placebo group; median PFS was 11.0 months versus to 5.7 months in the respective treatment arms (hazard ratio [HR] 0.65; 95% confidence interval [CI], 0.50-1.25; p = 0.00065). The objective response rate (ORR) was 36% in the alpelisib/fulvestrant arm versus 16% in the placebo/fulvestrant arm (p = 0.0002). The secondary endpoint of locally assessed PFS in patients without PI3KCA mutations did not meet the predefined proof of concept endpoint; median PFS was 7.4 versus 5.6 months, with alpelisib versus placebo, respectively (HR 0.85; 95% CI, 0.58-1.25).

The most frequent adverse events with alpelisib were hyperglycaemia, nausea, decreased appetite and rash. Five percent of patients on alpelisib and 1% of patients on placebo discontinued treatment due to adverse events. NCT02437318. André *et al.* Abstract LBA3-PR

Practice point and future research opportunities

This is the first trial to show a clinically relevant benefit with a PI3K inhibitor combined with endocrine therapy in patients with HR-positive, HER2-negative advanced breast cancer with PIK3CA mutations. Alpelisib plus fulvestrant therapy met the primary endpoint by significantly extending PFS compared to placebo plus fulvestrant and demonstrated a manageable tolerability profile. Findings from SOLAR-1 suggest that alpelisib offers the potential for increased life expectancy in patients with HR-positive, HER2-negative advanced breast cancer and PI3KCA mutations. However, the follow-up was short so the long-term survival benefit remains unknown. A further limitation of the study was that only a modest number of patients were pre-treated with CDK4/6 inhibitors, which had become a new standard of care in this setting. The next critical step will be to understand when, and how, this compound should be incorporated into the current treatment algorithm – upfront, in combination with endocrine therapy and a CDK4/6 inhibitor, or sequentially, after disease progression is observed with combination treatment of endocrine therapy and a CDK4/6 inhibitor.

Citation:

1. Mayer IA, Abramson VG, Formisano L, *et al.* A phase Ib study of alpelisib (BYL719), a PI3Kα inhibitor, with letrozole in ER+/HER2- metastatic breast cancer. *Clinical Cancer Research* 2017; 23:26-34.

Adjuvant zoledronic acid prolongs DFS in premenopausal women with HR-positive early breast cancer

Lead author Francesco Perrone, Istituto Nazionale Tumori in Naples, Italy presented promising results from the HOBOE-2 (Hormonal BOne Effects-2) study. Professor Perrone and colleagues were prompted to study the efficacy and safety of adjuvant zoledronic acid based upon the rationale that zoledronic acid modifies the bone microenvironment, which provides a niche where breast cancer micrometastases remain dormant; these microenvironment modifications may be lethal for isolated cancer cells, therefore reducing the risk of distant metastases over time. HOBOE-2 enrolled 1065 premenopausal patients, with last menses within one year, who had been treated with surgery and neoadjuvant or adjuvant chemotherapy for oestrogen/progesterone receptor positive early breast cancer. The women were randomised 1:1:1 to receive hormonal therapy with tamoxifen at 20 mg/day, or letrozole at 2.5 mg/day, or to zoledronic acid at 4 mg i.v. every six months plus letrozole at 2.5 mg/day for a planned treatment duration of five years. In addition, all women received triptorelin at 3.75 mg every 4 weeks to suppress ovarian function. Disease-free survival (DFS) events were defined as breast cancer recurrences or second breast or non-breast cancers, or deaths.

The study was stopped early in May 2018 when the Independent Monitoring Committee recommended sharing the data with the Early Breast Cancer Trialists' Cooperative Group (EBCTCG) 2018 overview. After a median follow-up of 65 months, 58 DFS events had occurred with tamoxifen and 44 with letrozole, compared to 32 DFS events with zoledronic

acid plus letrozole. The 5-year DFS probability was 0.85, 0.93, and 0.93 with the respective treatments (p = 0.008). Compared to tamoxifen, the DFS benefit with zoledronic acid plus letrozole was statistically significant (hazard ratio [HR] 0.52; 95% confidence interval [CI], 0.34-0.80; p = 0.003). Other comparisons were not statistically significant: letrozole versus tamoxifen (HR 0.72; 95% CI, 0.48-1.07; p = 0.06) and zoledronic acid plus letrozole versus letrozole (HR 0.70; 95% CI, 0.44 -1.12; p = 0.22). Zoledronic acid plus letrozole was more effective that the other treatments across all evaluated subgroups except the subgroup of women overexpressing HER2, who showed a stronger response to tamoxifen (interaction p = 0.002).

Adverse events occurred more frequently in patients receiving zoledronic acid/letrozole. Nine percent of these patients had grade 3/4 toxicity compared to 4% of those treated with tamoxifen, and 7% of patients receiving sole letrozole. Seventeen percent of patients on zoledronic acid plus letrozole stopped treatment before 5 years due to toxicity or refusal, compared to 7% of women receiving tamoxifen, and 7% receiving letrozole monotherapy. Four cases of jaw osteonecrosis were reported in the combination zoledronic acid/letrozole arm. NCT00412022. Perrone *et al.* Abstract LBA14_PR

Practice point and future research opportunities

Previous studies demonstrated that zoledronic acid plus hormonal therapy was associated with reduced breast cancer recurrence and mortality in hormone receptor (HR)-positive breast cancer in postmenopausal women, but the benefit in premenopausal women remained unclear. Findings from this study strongly support the hypothesis that combination treatment with an aromatase inhibitor and bisphosphonate plus triptorelin may improve prognosis in premenopausal patients with HR-positive breast cancer. However, this study was underpowered, with insufficient events for statistical confidence in the results. It is unlikely that further trials with aromatase inhibitors and bisphosphonates will be planned, as the focus is now on adding other targeted treatments. However, if these findings are confirmed with longer follow-up, this treatment may turn out to be a highly cost-effective treatment for premenopausal HR-positive breast cancer, since both zoledronic acid and letrozole are inexpensive compared to many cancer drugs.

Patient-reported outcomes favour talazoparib over physician's choice of chemotherapy treatment in patients with advanced breast cancer and a germline *BRCA1/2* mutation

Findings from a key subgroup analysis of patient reported outcomes (PROs) from the phase III open-label EMBRACA trial were presented by Hope S. Rugo, Breast Cancer Centre, UCSF Helen Diller Family Comprehensive Cancer Centre, San Francisco, USA. Previously reported results from this study showed a statistically significant improvement in median progression-free survival (PFS) in patients with advanced triple negative breast cancer (TNBC) and germline *BRCA* mutation (gBRCAm) of 5.8 with talazoparib compared to 2.9

months with physician's choice chemotherapy treatment (PCT; hazard ratio [HR] 0.60; 95%, confidence interval [CI] 0.41-0.87; p = 0.008).[1]

EMBRACA randomised 130 women with TNBC and gBRACm to talazoparib and 60 to PCT. The EORTC quality of life questionnaire-core (QLQ-C30) and the corresponding breast cancer module, QLQ-BR23 were administered and assessed at baseline, at the start of each 3-week treatment cycle, and end of treatment. Higher scores on both modules indicate better functioning, global health status (GHS), and quality of life (QoL), and higher scores on pain severity questions indicated worse symptom severity. Repeated measures mixed-effects analyses were performed to compare overall change from baseline scores in the cohorts. Time to definitive deterioration (TDD) was defined as a change of ≥10 points) in GHS/QoL and pain symptoms, which were compared using stratified log-rank test and Cox proportional hazards model.

While baseline scores were similar between arms, patients on talazoparib demonstrated a statistically significant overall change from baseline in GHS/QoL of 12.5 points over PCT (95% confidence interval [CI] 7.1-17.8; p < 0.0001). Talazoparib also provided statistically significant favourable differences in overall change from baseline in physical, role, social, and body image scores. Changes from baseline with talazoparib were also statistically significant for the decrease in symptoms including fatigue, pain, appetite loss, breast, and arm. No significant differences were observed between the talazoparib and PCT groups in the domains for emotional and cognitive functioning, nausea/vomiting, dyspnoea, insomnia, constipation, diarrhoea, upset by hair loss, sexual enjoyment, and functioning. Talazoparib treated patients demonstrated a statistically significant delay in TTD for GHS/QoL compared to patients on PCT; the median TTD was 24.3 compared to 4.5 months, respectively (hazard ratio [HR] 0.33; 95% CI, 0.19-0.57; p < 0.0001). Median TTD for pain was 4-fold longer with talazoparib than PCT at 22.7 versus 5.6 months (HR 0.25; 95% CI 0.14-0.45; p < 0.0001). NCT01945775. Rugo *et al.* Abstract 292O

Practice point and future research opportunities

Global Health and QoL scores were significantly improved with talazoparib therapy over physician's choice of chemotherapy treatment in patients with gBRCAm advanced TNBC. Time to deterioration was approximately 4 times longer with talazoparib for pain and GHS/QoL. Taken together with previously reported results demonstrating significantly longer PFS favouring talazoparib over PCT, talazoparib represents a promising new treatment in this setting.

Citation:

1. Abstract GS6-07 presented at the 2017 San Antonio Breast Cancer Symposium.

Ribociclib plus letrozole is well-tolerated by male patients with HR-positive, HER2-negative advanced breast cancer

Claudio Zamagni, Breast and Gynaecological Medical Oncology, Sant'Orsola Malpighi Hospital, Bologna, Italy presented preliminary safety findings from a subgroup of male patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer participating in the phase IIIb, open label CompLEEment-1 study. Twenty men with HR-positive, HER2-negative advanced breast cancer were among the first 1008 patients completing 56 days of follow-up or discontinuing the study prior to the data cut-off. All patients had received ≤1 line of prior chemotherapy, and no prior endocrine therapy for advanced breast cancer. They were treated with first-line ribociclib at 600 mg per day on a 3 weeks on/1 week off schedule, plus letrozole at 2.5 mg per day. The men and premenopausal women also received concomitant goserelin as a 3.6 mg subcutaneous implant every 28 days. This pre-planned interim analysis of safety and tolerability was conducted approximately 15 months after the first patient's first visit for the primary outcome. The median age of the patients was 63.5 years, all had an ECOG performance status ≤1, and 45.0% of patients had stage IV disease at diagnosis. The most common sites of metastasis were lung in 75.0%, lymph nodes in 40.0%, and liver in 20.0% of patients.

The safety data of the male subgroup revealed that the combination had comparable safety and tolerability when administered as first-line therapy in men with HR-positive, HER2-negative advanced breast cancer as has been reported in women. The most frequently reported adverse events (AEs) were hot flush in 30.0% of patients, neutropaenia in 20.0%, and 20% of male patients reported constipation. Grade ≥3 AEs included neutropaenia in 20% of patients, increased alanine aminotransferase in 10.0%, and increased aspartate aminotransferase in 5.0% of the male subgroup. Grades 1/2 QT prolongation occurred in 15.0% of patients and dose reduction or interruption due to AEs was required for 35.0% of the male cohort. Two men discontinued treatment due to AEs. NCT02941926. Zamagni *et al.* Abstract 293PD

Practice point and future research opportunities

Ribociclib is a CDK4/6 inhibitor that has been approved in combination with an aromatase inhibitor for the treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women who did not undergo previous treatment for advanced breast cancer. Approval was based upon the results of the pivotal phase III MONALEESA-2 trial, wherein PFS was significantly improved with the combination compared placebo plus letrozole.[1] However, the MONALEESA-2 trial did not include men with HR-positive, HER2-negative advanced breast cancer and there were no safety or tolerability data available for

male patients. It was necessary to evaluate the tolerability to this treatment in these patients due to the resistance to hormonal therapies that often develops over time.

From the data provided by this analysis of a subgroup of men, it appears that the tolerability and the expected toxicity with ribociclib in men is no different than that reported in female patients. Hormonal therapy plus ribociclib should be considered as an option for male patients with metastatic HR-positive, HER2-negative breast cancer. However, the study is limited by the small number of male patients and by the lack of available efficacy data with the combination treatment in men. The first step forward is to compare the outcome between the men and women in the CompLEEment study, as well as this safety data.

Citation:

1. Hortobagyi GN, Stemmer SM, Buris HA, *et al.* Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *NEJM* 2016; 375(18):1738–1748.

Metastatic breast cancer is managed similarly in men and women registered in the national multicentre observational ESME platform and provides equivalent outcomes

Although 1% of breast cancer occurs in men there have been few prospective studies in men, and clinical trials of breast cancer treatments have often excluded men, so treatment recommendations in male patients is extrapolated from the clinical trial results in women.[1] Junien Sirieix, Medical Oncology, Centre Hospitalier Régional Universitaire de Tours in Tours, France, presented treatment and outcome findings from one of the largest series of men treated for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer. The team of French researchers reviewed clinical data collected by the Epidemiological Strategy and Medical Economics Metastatic Breast Cancer (ESME MBC) platform from January 2008 to December 2014.

The data included all patients newly diagnosed with MBC who began at least one treatment during this time. The investigators then compared the treatment and outcome in 149 men with MBC with that in 16,701 women in the database. In comparison with the women, male patients were older with a mean age of 68.1 years versus 60.6 years in the female cohort ($p < 0.0001$). The proportion of males (78.4%) with HR-positive, HER2-negative breast cancer was also higher than in women (65.6%; $p = 0.0019$).

This analysis of ESME data showed that both men and women received similar treatment for metastatic HR-positive, HER2-negative breast cancer and had comparable outcomes. Forty-five (42.9%) male patients received front-line hormonal therapy comprising tamoxifen in 20 men, an aromatase inhibitor plus luteinizing hormone releasing hormone analogues in 18, and 7 men received other therapy. This cohort had median progression-free survival (PFS) of 9.8 months, compared to 13 months in a matched group of women ($p = 0.8$) with the same age, breast cancer histology, and grade, location of metastasis, and adjuvant treatment. Twenty-nine (27.6%) men with HR-positive, HER2-negative breast cancer

received front-line chemotherapy. The PFS was similar to a matched group of women also treated with chemotherapy; median PFS was 6.9 months compared to 6.3 months, respectively (hazard ratio [HR] 1.24; 95% confidence interval [CI], 0.69-2.23).

Overall survival for the entire population of men included in the database was 41.8 months compared to 34.9 months in women (p = 0.745).

This study is ongoing and will next assess the prevalence of *BRCA* mutation in both genders in the patient population. More information is needed to improve the customised management of MBC in men. Sirieix *et al.* Abstract 294PD

Practice point and future research opportunities

Extensive data on advanced breast cancer in men such as this was missing until now. This new study shows men and women have a similar prognosis, which is of great value as this justifies and supports the current clinical practice of treating men with breast cancer in a similar way to women. Although this is the largest study of its kind, this series was limited by being based on a small cohort of men and the lacking data regarding the extent of advanced disease, *BRCA* mutation status, and the type of chemotherapy used.

Citation:

1. Giordano SH. Breast cancer in men. *NEJM* 2018; 378:2311-20.

The Male-GBG54 study directly compared the effects of three endocrine treatments on oestradiol levels in men with HR-positive breast cancer

Mattea Reinisch, Klinikum Essen-Mitte, Essen, Germany, presented the final results from the Male-GBG54 study, which is the first prospective randomised trial to evaluate different endocrine treatments in men with breast cancer. Professor Reinisch explained that hormone receptor (HR)-positive disease is present in 90% of male breast cancer patients, which formed the rationale for this study. Tamoxifen is the current standard of hormonal care for HR-positive disease, but there is a paucity of data regarding efficacy and safety in men and information on other hormone blocking treatments is even more sparse. The investigators randomly assigned 55 men with breast cancer to receive endocrine therapy comprising tamoxifen at 20 mg per day, tamoxifen plus gonadotrophin releasing hormone (GnRH) analogue subcutaneous every 3 months, or exemestane at 25 mg dayly plus GnRH analogue as (neo)adjuvant or metastatic therapy for six months.

Tamoxifen blocks oestrogen from attaching to HRs on cancer cells while exemestane is an aromatase inhibitor that inhibits oestrogen synthesis. The use of GnRH analogues in men with breast cancer is controversial but is based on reduced levels of testosterone when used in combination with aromatase inhibitors or antiandrogens.

The primary objective was oestradiol suppression after 3 months of treatment and secondary objectives included oestradiol suppression after 6 months and levels of different steroidal hormones after 3 and 6 months. With tamoxifen monotherapy, the median level of oestradiol increased by 67% at 3 months and by 41% at 6 months. The greatest degree of oestradiol suppression was seen with tamoxifen plus a GnRH analogue where levels decreased by 85% after 3 months and by 59% at 6 moths in the male patients. Men treated with a GnRH analogue plus exemestane demonstrated a 73% oestradiol decrease at 3 months and of 63% at 6 months. All therapies were well tolerated and no safety signals were raised.

The impact of treatment on quality of life and sexual function in men with breast cancer following hormonal therapy was evaluated in this study for the first time, using the Aging Males' Symptoms Scale Questionnaire and assessment of erectile function, according to the International Index of Erectile Function. This assessment showed that tamoxifen had little impact on health-related quality of life or erectile function in men with breast cancer while the combination of GnRH analogue plus exemestane had a major adverse effect on both measures. NCT01638247. Reinisch *et al.* Abstract 273PD

Practice point and future research opportunities

The authors are to be congratulated for conducting a randomised trial in such a rare study population. However, it is regrettable that the oestradiol suppression at 3 months was the primary endpoint. Although it is relevant to know whether and to what extent oestradiol levels change over time during different endocrine treatment strategies, oestradiol suppression at 3 months is neither a validated nor a clinically useful surrogate endpoint for the efficacy of endocrine treatment. These data suggest that tamoxifen should remain the treatment for men with HR-positive breast cancer due to the lack of adverse effects on quality of life or erectile function, as compared to the deleterious impact seen with GnRH analogue plus exemestane on both measures.

CNS TUMOURS

Intra-CSF liposomal cytarabine plus systemic therapy as initial treatment of patients with breast cancer leptomeningeal metastasis improves PFS but not OS

Emilie Le Rhun, Breast Cancer Unit, Oscar Lambret Centre, Lille, France remarked that the role of intra-cerebrospinal fluid (CSF) therapy for the treatment of leptomeningeal metastasis (LM) remains controversial. Therefore, Professor Le Rhun and colleagues carried out this multicentre randomised open-label study to investigate the effect of adding liposomal cytarabine to systemic therapy for treating LM from breast cancer. Patients were eligible when tumour cells could be detected in the CSF or typical clinical and magnetic resonance imaging (MRI) signs of LM. The patients were randomised to standard systemic therapy alone (n=37) and 36 patients received systemic therapy plus 5 injections of intra-CSF liposomal cytarabine at 50 mg for 2 weeks, followed by monthly injections of 50 mg until progression or unacceptable toxicity occurred, or for 1 year. The investigators performed neurological and quality of life evaluation monthly and cerebrospinal MRI every 2 months. The primary endpoint was investigator-assessed progression-free survival in the leptomeningeal compartment (LM-PFS), and overall survival (OS) was a secondary efficacy endpoint. Baseline characteristics were well matched in both arms.

The patients receiving cytarabine had a median of 5 (range, 1-20) liposomal cytarabine injections. Focal radiotherapy was done in 16% of patient on systemic therapy and 14% of patients receiving cytarabine. With systemic therapy alone, the median LM-PFS was 2.0 months (95% confidence interval [CI], 1.3-2.7) compared to 4.3 months (95% CI, 2.3-5.7) with systemic therapy plus cytarabine (hazard ratio [HR] 0.57; 95% CI, 0.35-0.92; p = 0.02). In the intent-to-treat population, 68 patients died. The actuarial median OS was 4.0 months (95% CI, 2.2-6.5) with systemic therapy versus 7.3 months (95%CI 3.9-12.6) with added cytarabine (HR 0.80; 95% CI, 0.50-1.29; p = 0.35). Serious adverse events were reported in 6 and 14 patients in the respective treatment groups. NCT01645839. Le Rhun *et al.* Abstract 371O

Practice point and future research opportunities

Adding liposomal cytarabine to systemic therapy may improve LM-related PFS but did not significantly improve OS. A longer follow-up and a larger study may aid in determining whether there is a clinical benefit. Quality of life data will also inform the decision to add cytarabine to systemic treatment in breast cancer patients with LM.

Mutational and inflammatory microenvironment characteristics investigated in primary and matched local recurrent brain metastases from NSCLC

Since the majority of patients with brain metastases (BM) develop brain relapse during their clinical course, Anna Sophie S. Berghoff, Department of Medicine 1, Medical University of

Vienna in Vienna, Austria and colleagues aimed to investigate the mutational and immunological heterogeneity in BM, which are both putative drivers of treatment resistance and tumour progression. Their study identified patients who had undergone neurosurgical resection of a newly diagnosed BM from non-small cell lung cancer (NSCLC) and subsequent neurosurgical resection of the local BM recurrence in the Vienna Brain Metastasis Registry. They then performed whole exome sequencing and an analysis of tumour infiltrating lymphocytes (TILs) using immunohistochemistry on 24 matched BM specimens obtained from 12 patients. Seventy-five percent of patients were male, with a median age of 60 years.

When comparing the two specimens from the same patient the investigators found high concordance in CD3+ TIL ($p = 0.004$) and CD8+ TIL ($p = 0.004$) density, as well as in the tumour mutational burden (TMB; $p < 0.001$). One case (8.3%) changed from low CD3+ and CD8+ TIL density to high density, although no radiotherapy or immunotherapy was applied in-between the change. TMB in the first resection specimen, with a median 39.2 mutations/Mb correlated with TMB in the second resection specimen of 39.3 mutations/Mb ($p < 0.001$). Another single case (8.3%) presented with a marked TMB increase (154 mutation/Mb to 217 mutation/Mb) after application of stereotactic radiotherapy to the resection cavity. No association was determined between TIL density and TMB in 5 investigated sets of specimens ($p > 0.05$). Overall the mutational characteristics were stable between the two specimens at the same location but at different time points of the same patients as 88% (range 80%-93%) of mutations were shared by both samples. Berghoff *et al.* Abstract 372O

Practice point and future research opportunities

In this study, the investigators found high concordance in mutational and immunological characteristics in a homogenous cohort of local NSCLC brain metastasis recurrences. Both TIL density and TMB were consistent between the BM and the matching local recurrence. Radiotherapy may impact the mutational characteristics. These interesting first findings require further analysis of the mutational differences, which may inform new therapeutic approaches for secondary BM prevention.

DEVELOPMENTAL THERAPEUTICS

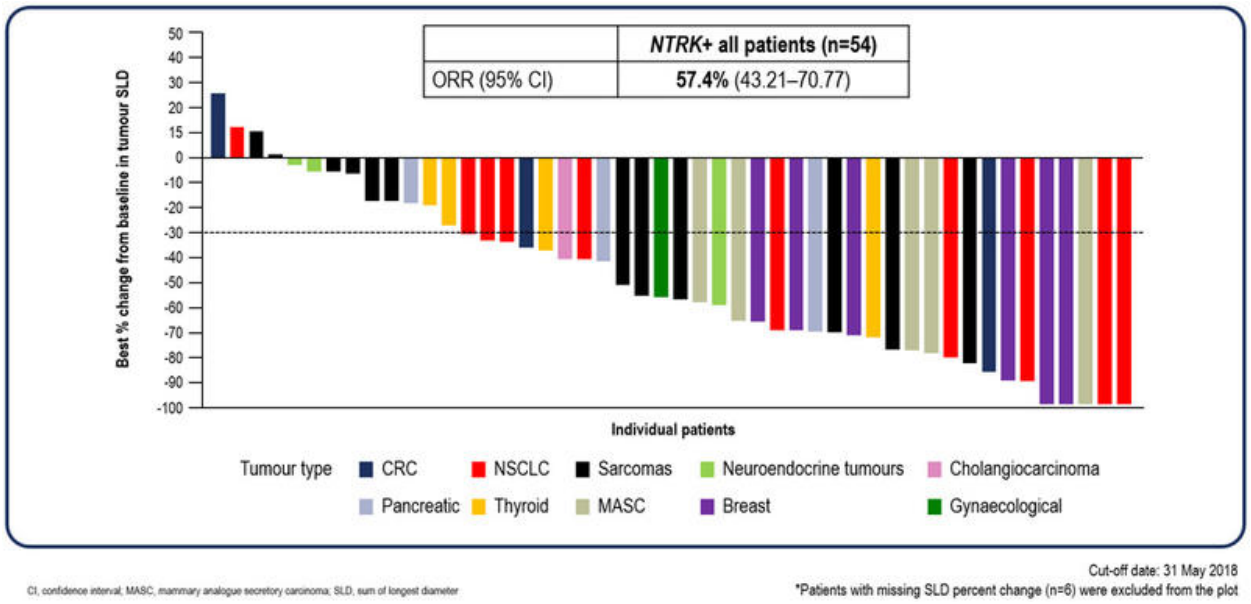
Analysis of pooled data from 3 trials shows entrectinib is effective across various *NTRK* fusion positive solid tumour types

Lead author Professor George D. Demetri, Centre for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute in Boston, USA, presented an integrated efficacy and safety analysis from three phase I/II clinical trials of entrectinib: ALKA, STARTRK-1, and STARTRK-2. Entrectinib is a CNS-active, potent inhibitor of all TRK proteins (TRKA/B/C) as well as ROS1 and ALK. Neurotropic tropomyosin receptor kinase (*NTRK*) gene fusions lead to the transcription of chimeric TRK proteins that have uncontrolled kinase function, which confers oncogenic signals across several tumour types.

The 3 studies in the analysis enrolled patients from more than 150 global sites in 15 countries. The patients had metastatic and/or locally advanced solid tumours that harboured NTRK-fusions that were confirmed by nucleic acid-based methods. Tumour assessment was done after 4 weeks of treatment and every 8 weeks thereafter. Scans were evaluated by blinded independent central review (BICR) using RECIST v1.1. The primary endpoints of the trials were overall response rate (ORR) and duration of response (DoR) by BICR, and secondary endpoint included safety, progression-free survival (PFS), and overall survival (OS) in patients with and without baseline CNS disease. This tumour agnostic efficacy analysis included 54 adult patients with a minimum of six months follow-up of advanced or metastatic *NTRK*-fusion positive solid tumours, comprising more than 19 histopathologies involving 10 general tumour types. Patients with baseline CNS metastasis were allowed to enrol.

Entrectinib treatment induced responses that were durable in more than half of patients with solid tumours and *NTRK* rearrangements (Figure). Per BICR, the ORR was 57.4% (95% confidence interval [CI], 43.2-70.8%), which included 4 (7.4%) complete responses. Responses were observed across all tumour types (see visual waterfall plot of data).

Figure: Entrectinib induces objective responses in the majority of patients across multiple types of solid tumours harboring *NTRK*-fusions, both with and without cancer involvement of the CNS. Individual ORR by tumour type: patients with NTRK fusion positive solid tumours (integrated analysis population; BICR).



© George D. Demetri

The median DoR was 10.4 months (95% CI, 7.1-not reached [NR]), median PFS was 11.2 months (95% CI, 8.0-14.9), all by BICR, and median OS was 20.9 months (95% CI, 14.9-NR). The median follow-up for survival in these patients was 12.9 months.

Data evaluation by investigator-assessed status of metastatic spread to the CNS at baseline revealed consistent responses both in patients without baseline CNS metastases (n=42; ORR 59.5%) and in patients with metastatic cancer to the CNS (n=12; ORR 50%). Additionally, the intracranial response (IC-ORR) was 54.5% in patients with CNS disease at baseline, as assessed by BICR, was observed to be similar to systemic response rates, including 3 intracranial complete responses. The safety population included all 355 patients treated with entrectinib across the 3 clinical trials. Overall, entrectinib was tolerable with a manageable safety profile. Most treatment-related adverse events (TRAEs) were grades 1–2 and were managed with dose reduction (27.3%) or dose interruption (25.4%); 3.9% of patients discontinued entrectinib due to TRAEs.

In 2017, the US Food and Drug Administration granted a breakthrough therapy designation to entrectinib for use as a treatment for adult and paediatric patients with *NTRK*-fusion positive, locally advanced or metastatic solid tumours who have either progressed following prior therapies or who are not eligible for standard therapies. The Priority Medicines (PRIME) designation from the European Medicines Agency has also been received in 2017, and SAKIGAKE designation in Japan in March 2018. ALKA (EudraCT 2012-000148-88),

STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267). Demetri *et al.* Abstract LBA17

Practice point and future research opportunities

This new dataset focuses on the key TRK fusion population. It would be interesting to determine whether there is any contribution to efficacy from other fusions and if TRK is mutually exclusive with ALK and ROS. The PFS of around 11 months is encouraging, and the CNS activity is highly encouraging and offers significant potential clinical benefit.

GSK2636771 shows modest activity in various cancer types with PTEN mutation/deletion or PTEN protein loss in the NCI-MATCH trial

Filip Janku, Investigational Cancer Therapeutics, MD Anderson Cancer Centre, Houston, USA presented findings from the phase II NCI-MATCH trial, which encompasses 1173 sites, making it the largest precision medicine study for patients with relapsed/refractory solid tumours, lymphomas and myeloma. In the trial, targeted therapies are assigned to patients based on the individual tumour molecular alterations detected using the adapted Oncomine AmpliSeq panel (143 genes) and immunohistochemistry (IHC). NCI-MATCH is investigating whether targeted therapies can be assigned based on the presence of certain gene mutations rather than by cancer type. Particularly, the investigators evaluated the efficacy of the PI3K beta-selective inhibitor GSK2636771 in patients with PTEN-deficient cancers.

The trial launched in August 2015 and has nearly 40 treatment arms; Professor Janku presented findings from arms N and P. Both arms enrolled patients with relapsed/refractory cancer, good end-organ function, who had been screened for molecular alterations by centralised testing on fresh tumour biopsy. Arm N patients had deleterious PTEN mut/del without loss of expression and arm P contained patients with tumours demonstrating complete loss of cytoplasmic and nuclear PTEN staining by IHC. Patients were required to have no other aberrations that could activate the PI3K/MTOR and MAPK pathways, which included mutations in *PIK3CA, PIK3R1, BRAF, KRAS, AKT1, TSC1/2, mTOR, RHEB, NF2, NRAS,* and *HRAS* genes. In both arms, GSK2636771 was administered at 400 mg per day in 28-days cycles. The primary endpoint was overall response rate (ORR) per RECIST v1.1.

In the 56 patients overall, median progression-free survival was 1.8 months. Arm N comprised 22 patients with PTEN mutt/del; of these, 6 patients had uterine tumours, 2 had breast, 2 had prostate, 2 had head and neck cancer, 10 patients had other cancers. All patients were off treatment by the time of this analysis; 14 due to disease progression, 4 due to adverse events [AEs], and 4 patients cited other reasons. The efficacy results showed the ORR was 4.5% based on one patient with prostate cancer and PTEN deletion, MPRSS2-ERG fusion, attaining a partial response (-42%). Seven (32%) patients achieved stable disease (SD), which lasted for >6 months in one patient with uterine leiomyosarcoma, and one with endometrial carcinoma. Thirty percent of arm N patients had grade ≥3 treatment-related reversible toxicities.

In the 34 patients with loss of PTEN protein by IHC in arm P, 7 patients had prostate cancer, 6 had breast, 3 had squamous anal cancer, 2 had cholangiocarcinoma, and 16 patients had other cancer types. All patients were off treatment at the analysis, 26 due to disease progression, 4 because of AEs, and 4 patients due to other causes. SD was achieved by 9 (37.5%) patients; of these the DoR of SD was >6 months in 3 patients, each of whom had prostate cancer; squamous bladder cancer, and squamous anal cancer. Twenty percent of patients had grade ≥3 treatment-related reversible toxicities.

NCT02465060. Janku *et al.* Abstract 418PD

Practice point and future research opportunities

NCI-MATCH represents the first attempt to systematically leverage next-generation sequencing to explore many therapies in parallel. However, in arms N and P, single agent GSK2636771 demonstrated very modest activity in cancer types with PTEN gene mutation/deletion and/or PTEN protein loss.

ENDOCRINE TUMOURS

Potential therapeutic targets identified in recurrent and metastatic parathyroid carcinomas by next-generation sequencing

Ming Cui, Department of General Surgery, PUMCH, Beijing, China and colleagues aimed to identify potential therapeutic targets for parathyroid carcinoma, which is a rare endocrine malignancy. Parathyroid carcinoma is effectively managed by complete surgical resection; however, treatment options are limited for inoperable disease, and in recurrent or metastatic disease, which occur at a high rate. The investigators used next generation sequencing (NGS) to identify drug targets that may predict the efficacy of available drugs. They extracted DNA from formalin-fixed, paraffin-embedded (FFPE) sections of 19 recurrent or metastatic patient samples. A panel of 560 genes was sequenced with NGS using Illumina HiSeq X platform to identify genomic alterations at an average sequencing depth of 581×, which detected 190 genomic alterations. Nine (47%) parathyroid carcinoma samples had at least one potentially actionable genomic alteration including, *ROS1* (26%), *PTEN* (16%), *TSC1* (11%), *PIK3CA* (5%), *AKT1* (5%), *MTOR* (5%), *ERBB2* (5%), *NTRK1* (5%), *IDH1* (5%), and *FGFR3* (5%). *CDC73* mutations were detected in 47% of parathyroid carcinoma samples. Additional recurrent genomic alterations were identified in *MSH2* (79%), *AR* (47%), *BCR* (42%), *SLC45A3* (32%), *MAGI1* (26%), *ZNF521* (21%), *KMT2C* (21%), and *NOTCH4* (21%). Cui *et al.* Abstract 450PD

Practice point and future research opportunities

This study identified for the first time large numbers of potentially actionable genomic alterations that occurred at a high frequency in samples from patients with parathyroid carcinoma, as well as a series of recurrently occurring mutant genes. These findings may aid to inform the selection of novel targeted therapies for these patients and may contribute to the molecular understanding of parathyroid carcinoma.

Greater lenvatinib efficacy observed in patients with radioiodine-refractory differentiated thyroid cancer and slow tumour growth rate

Lead author Sophie Leboulleux, Gustave Roussy, University Paris-Saclay, Villejuif, France discussed the heterogeneity found among patients with differentiated thyroid cancer (DTC). Professor Leboulleux and colleagues evaluated the relationship between tumour growth rate (TGR), which is correlated with life expectancy, and the lenvatinib efficacy in this post hoc, exploratory analysis of data from the phase III SELECT trial. Eligible patients in SELECT had independent radiologic evidence of progression within 13 months prior to randomisation (prebaseline) to lenvatinib or placebo. Pre-randomisation TGR was assessed per each patient as the sum of target lesions at baseline minus the sum of target lesions at prebaseline divided by the sum of target lesions at prebaseline, and then divided by the interval in months between the 2 examinations. Patients were stratified according to slow TGR (TGR ≤ median TGR of all SELECT patients) and fast TGR (TGR > median). The

patients were further categorised as to baseline liver metastases (yes versus no), age (≤65 versus >65 years), histology (papillary versus follicular), ECOG performance status (PS, 0 versus ≥1), and baseline thyroid-stimulating hormone (TSH) (≤0.1 versus >0.1 uIU/mL).

In a multivariate model, the TGR of patients receiving lenvatinib was significantly associated with baseline tumour size, and baseline metastases to the liver, bone, and other locations. Lenvatinib improved progression-free survival (PFS) compared to placebo in patients having slow TGR, where median PFS was 20.2 versus 3.7 months, respectively (hazard ratio [HR] 0.19; 95% confidence interval [CI], 0.12-0.32; $p < 0.001$). PFS was also improved with lenvatinib in the fast TGR groups, where median PFS was 14.8 versus 3.5 month with lenvatinib versus placebo (HR 0.20; 95% CI, 0.12-0.33; $p < 0.001$). PFS in patients on lenvatinib was significantly longer in the slow versus fast TGR group, where median PFS was 20.2 versus 14.8 months, respectively (HR 0.62; 95% CI, 0.41-0.94; $p = 0.0232$). Other patient characteristics, including age, ECOG PS, and baseline TSH levels also affected PFS demonstrated in the slow and fast TGR groups.

Overall survival (OS) was improved with lenvatinib compared to placebo in the slow TGR cohort where median OS was not reached (NR); (HR 0.53; 95% CI, 0.29-0.97), and in the fast TGR groups, median OS was NR with lenvatinib versus 20.3 months with placebo (HR 0.78; 95% CI, 0.43-1.39). However, OS in the fast TGR group did not reach significance. Patients receiving lenvatinib in the fast and slow TGR cohorts demonstrated similar OS (HR 0.77; 95% CI, 0.46 – 1.29). NCT01321554. Leboulleux *et al.* Abstract 1819O

Practice point and future research opportunities

Lenvatinib was approved for radioiodine-refractory DTC based on the results of the phase III SELECT trial. This post hoc analysis confirmed that lenvatinib had clinical benefit over placebo for all patients regardless of tumour growth rate; however, this benefit was greatest, as depicted by the PFS, which was significantly longer in patients with slower TGR.

GASTROINTESTINAL TUMOURS, COLORECTAL

Combined nivolumab and ipilimumab proposed as **first-line treatment in** microsatellite instability-high/mismatch repair deficient **metastatic colorectal cancer**

Heinz-Josef Lenz, University of Southern California Norris Comprehensive Cancer Centre in Los Angeles, USA presented the first efficacy and safety results from the CheckMate-142 trial wherein the combination of nivolumab and ipilimumab was administered as front-line in a cohort of treatment-naïve patients with microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal (mCRC). Previously reported second-line results of treatment with this combination in this study demonstrated durable clinical benefit in patients with MSI-H/dMMR mCRC that had received prior chemotherapy; an objective response rate (ORR) of 55%, duration of response (DoR) was not reached (NR), and the 12-month overall survival (OS) rate was 85% in that report.[1]

In this cohort of the phase II CheckMate-142 trial, patients having received no prior treatment for MSI-H/dMMR mCRC were treated with nivolumab at 3 mg/kg every 2 weeks plus low-dose ipilimumab every 6 weeks until disease progression. Of these 45 patients, 51% were male and the median age was 66 years. The primary endpoint was investigator assessed ORR per RECIST v1.1.

After a median follow-up of 13.8 months (range, 9 to 19 months) the ORR was 60% following combination immunotherapy, with 3 (7%) patients achieving complete response. Partial response was seen in 53% of patients, and 24% showed stable disease. The disease control rate (DCR) was 84%, with just 13% of patients experiencing disease progression after treatment with nivolumab plus ipilimumab. Responding patients demonstrated a median DoR of NR. The 12-month progression-free survival (PFS) and OS rates were 77% and 83%, respectively. Treatment-related adverse events (TRAEs) grade 3/4 occurred in 16% of patients. Any grade select immune-mediated TRAEs affecting the hepatic (13%), gastrointestinal (11%), pulmonary (2%), and renal (2%) systems resolved in 100% of patients. Toxicities affecting the skin (33%), and endocrine (24%) systems resolved in 45% and 60% of patients, respectively. Treatment was discontinued in 7% of patients due to TRAEs. NCT02060188. Lenz *et al.* Abstract LBA18_PR

Practice point and future research opportunities

Findings from the CheckMate-142 trial demonstrated that combined nivolumab and ipilimumab administered in the first-line setting provided durable responses in patients with MSI-H/dMMR mCRC. Previously, this trial showed that immunotherapy with nivolumab and low-dose ipilimumab provided durable clinical benefit and manageable side effects in patients with MSI-H mCRC that is resistant to chemotherapy, which led to approval by the US FDA. These findings may lead to a submission for approval of this immunotherapy combination in the first-line setting, although additional results from phase III studies will

most likely be required by licensing authorities. Other trials have tested high-dose ipilimumab combined with nivolumab, but CheckMate-142 used low-dose ipilimumab with nivolumab, which resulted in less toxicity. This study has the potential to provide a new standard of care for this patient population.

Citation:

1. Overman MJ, Lonardi S, Wong KYM, *et al*. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer, *JCO* 2018; 36:773–779.

Adding atezolizumab to standard maintenance with fluoropyrimidine plus bevacizumab does not improve outcome in patients with BRAF wild type metastatic colorectal cancer

Axel Grothey, Division of Medical Oncology, West Cancer Centre, Germantown, USA underscored the importance of using molecular screening approaches to identify new biomarkers, to fully characterise tumours, and to identify patients with metastatic colorectal cancer (mCRC) and wild-type *BRAF* that are most likely to benefit from targeted therapies. He presented findings from MODUL, a biomarker driven study, that is a highly adaptable, phase II signal seeking trial that evaluates the theory of tumoural heterogeneity under induction chemotherapy via switch maintenance treatment in first-line mCRC.

The ongoing MODUL study has an umbrella design that enrols patients with measurable, unresectable, previously untreated mCRC to be treated with 16 weeks of induction treatment consisting of FOLFOX plus bevacizumab. After induction, patients were randomised to maintenance comprised of either the standard of care, fluoropyrimidine (FP) plus bevacizumab (control), or one of four experimental maintenance regimens. At ESMO 2018 Congress, the results of cohort 2, which contained patients with BRAF wild-type who received maintenance therapy with FP/bevacizumab plus atezolizumab. The primary efficacy endpoint was progression-free survival (PFS, per investigator), and secondary endpoints included overall survival (OS), best overall response rate (ORR), disease control rate (DCR), time to treatment response (TTR); duration of response (DoR), ECOG performance status (PS), and safety.

In MODUL, 824 patients were screened and 696 received induction treatment. The 445 patients with BRAF wild-type mCRC were randomised to maintenance treatment in cohort 2; of these, 297 patients were treated with FP/bevacizumab plus atezolizumab and 148 controls received FP/bevacizumab. The primary analysis of cohort 2 patients, which was done after a median follow-up of 10.5 months, showed that the PFS endpoint was not met (hazard ratio [HR] 0.92; 95% confidence interval [CI], 0.72-1.17; p = 0.48) and OS data were immature. The ORR, DCR, TTP and DoR showed small numerical differences in favour of the experimental treatment. Subgroup treatment interactions were observed for gender, ECOG PS, response at end of induction, and the initial diagnosis (synchronous versus metachronous disease). In the updated analysis done after a median follow-up of 18.7

months, the PFS outcome remained unchanged (HR 0.96; 95% CI, 0.77-1.20; p = 0.727). The OS events were observed in 51% of patients (HR, 0.86; 95% CI, 0.66-1.13; p = 0.28). The safety profiles observed were consistent with previous findings and no new safety signals were observed. NCT02291289. Grothey *et al.* Abstract LBA19

Practice point and future research opportunities

The design of the MODUL trial permits future adaptation of current cohorts and the addition of new cohorts that allows for a number of therapies to be tested. However, the results from cohort 2 demonstrate that adding atezolizumab to the standard of care as first-line maintenance treatment for patients with BRAF wild-type mCRC did not improve efficacy outcomes or extend PFS.

DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with DPYD variants improves patient safety and is cost effective

Linda M. Henricks, Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands, highlighted the importance of screening for the dihydropyrimidine dehydrogenase (DPD) variants, which occur in approximately 30% of patients treated for cancer thus putting them at risk of severe, potentially fatal toxicity to fluoropyrimidines. While fluoropyrimidines are generally well-tolerated drugs, patients harbouring genetic DPYD variants have reduced activity of the key metabolising enzyme, DPD, resulting in reduced metabolism of fluoropyrimidines, the likely cause of toxicity. Professor Hendricks and colleagues conducted this prospective clinical trial to investigate whether the toxicity of fluoropyrimidine treatment can be reduced by upfront screening for 4 relevant DPYD variants and employing DPYD genotype-guided dosing.

Before initiating fluoropyrimidine therapy, 1,103 patients underwent prospective genotyping for DPYD*2A, c.2846A>T, c.1679T>G and c.1236G>A. Heterozygous DPYD variant carriers received an initial dose reduction of 25% (c.2846A>T, c.1236G>A) or 50% (DPYD*2A, c.1679T>G). The incidence of severe (grade ≥3) toxicity in DPYD variant carriers was compared to a historical cohort of DPYD variant carriers treated with full dose. Genotyping identified 85 (7.7%) patients as heterozygous DPYD variant carriers, who showed an overall frequency of grade ≥3 toxicity of 39%. The comparison of the incidence of toxicities in this cohort to toxicities in the historical cohort showed that DPYD genotype-guided dosing markedly reduced the risk of grade ≥3 toxicity for DPYD*2A and c.1679T>G carriers who received a 50% dose reduction and risk was moderately reduced for c.2846A>T carriers, who received 25% dose reduction. The risk of toxicity remained the same for c.1236G>A carriers, who also received a 25% dose reduction. Pharmacokinetic analyses showed that the fluoropyrimidine exposure after dose reductions in DPYD variant carriers was comparable to that observed in wild-type patients. A cost analysis showed that the reduced risk in toxicity resulted in average total treatments costs per patient that were lower for the screening strategy (2599 EUR) compared to non-screening (2650 EUR).

NCT02324452. Published simultaneously in the *Lancet Oncology*.[1] Henricks *et al.* Abstract. 452O

Practice point and future research opportunities

Upfront DPYD genotyping allowed for identification of heterozygous DPYD variant carriers, and the subsequent dose reduction in these patients improved patient safety during fluoropyrimidine chemotherapy. Moreover, genotypic screening is feasible in routine practice and is cost saving. A 50% initial dose reduction in fluoropyrimidines is recommended for heterozygous DPYD*2A and c.1679T>G carriers. Dose reduction of 25% used in this study for c.1236G>A and c.2846A>T carriers was not sufficient to lower the risk of severe toxicity in this group, so more cautious dose reductions of 50% are recommended by the investigators.

Citation:

1. Henricks LM, Lunenburg CATC, de Man FM, *et al. DPYD* genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncology* 2018; 19(11):1459-1467.

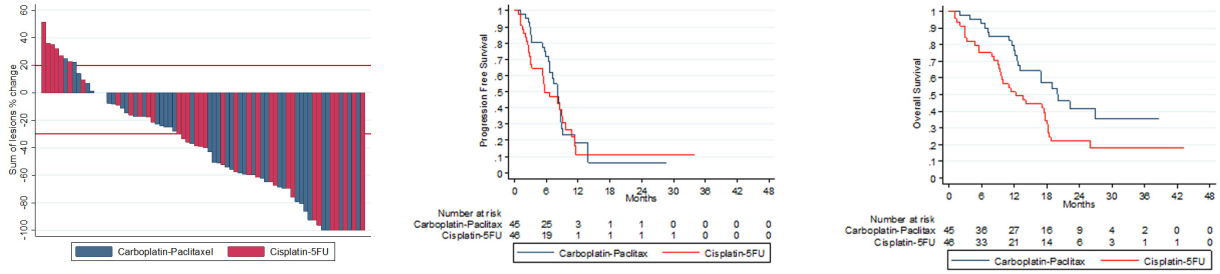
Carboplatin plus paclitaxel represents a new standard of care for patients with squamous cell carcinoma of the anal canal

Sheela Rao, Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom reported results on behalf of an international team of investigators. Professor Rao noted that, although advanced squamous cell carcinoma of the anal canal (SCCA) is a rare disease, the incidence has risen by 2% per year over the past decade. The medical need is heightened in this disease since there currently is no consensus on management, leaving SCCA patients with poor overall survival (OS).

The research team conducted this randomised phase II, selection trial with pick the winner design that aimed to establish a standard of care. In this trial, standard first-line therapy of fluoropyrimidine (5-FU) plus platinum agents was compared with taxanes, which have shown activity in this patient population. From 2014 to 2017, the InterAACT investigators enrolled 91 patients with inoperable locally recurrent or metastatic, treatment-naïve SCCA from more than 50 international centres. The patients were randomised equally to receive cisplatin at 60 mg/m^2 on day one of a 21 day cycle plus 5-FU at 1000 mg/m^2 over 24 hours on day one 4 times during the cycle, or to be treated with carboplatin at AUC 5 on day 1 every 28 days and paclitaxel at 80 mg/m^2 on days 1, 8, 15 every 28 days. The patients were stratified according to performance status, extent of disease, HIV status, and country. Overall, 67% of patients were women with a mean age of 61 years; 12% of patients had locally advanced, and 88% had metastatic disease. The primary endpoint was response rate (RR), and secondary endpoints included progression-free survival (PFS), OS, toxicity, quality of life (QoL), and feasibility.

The RRs to treatment were 57.1% with cisplatin/5-FU compared to 59.0% with carboplatin/paclitaxel. However, survival was prolonged with carboplatin/paclitaxel (Figure). Median PFS was 5.7 months for cisplatin/5-FU versus 8.1 months for carboplatin/paclitaxel (p = 0.375) and median OS with the respective treatments was 12.3 versus 20 months, hazard ratio [HR] 2.0 (p = 0.014).

Figure: The data establish carboplatin/paclitaxel as a standard of care for advanced treatment naïve anal cancer and this regimen can be employed as a cytotoxic platform for future combination trials



© Sheela Rao

Grade ≥3 toxicity was reported in 32 (76%) patients on cisplatin/5-FU and 30 (71%) patients on carboplatin/paclitaxel. The incidence of serious adverse events (SAEs) was lower with carboplatin/paclitaxel; SAEs were reported in 62% of cisplatin/5-FU patients compared with 36% of patients receiving carboplatin/paclitaxel (p = 0.016). NCT02051868. Rao *et al.* Abstract LBA21

Practice point and future research opportunities

Prior to InterAACT, no randomised trial in SCCA had been completed and this study has successfully demonstrated the feasibility of international collaboration in a rare cancer. The authors recommend that carboplatin/paclitaxel become a standard of care for first-line treatment of advanced SCCA, based upon the similar response rate demonstrated by carboplatin/paclitaxel compared to cisplatin/5-FU; however, less toxicity was observed with carboplatin/paclitaxel and thus was declared the winner. These findings establish carboplatin/paclitaxel as a standard of care for first-line treatment of advanced SCCA, and suggest that carboplatin/paclitaxel may serve as a backbone for the addition of novel agents in future phase II/III trials.

The investigators' conclusions are based on a small randomised, phase II trial, powered for a "pick the winner" design for ORR. In 1986, a prospective randomised trial was demanded to establish surgery-free treatment; however, this study has never been done and primary chemotherapy/radiotherapy is considered as a standard of care. The investigators are to be congratulated for their important work in establishing carboplatin/paclitaxel in patients with inoperable, locally recurrent or metastatic treatment naive anal cancer. This multinational effort should continue. It remains to be seen whether the recent results with nivolumab for

previously treated unresectable metastatic anal cancer or other immune checkpoint inhibitors will add to this.

GASTROINTESTINAL TUMOURS, NON-COLORECTAL

Trifluridine/tipiracil significantly prolongs OS versus placebo in patients with refractory metastatic gastric cancer

Hendrik-Tobias Arkenau, Sarah Cannon Research Institute, London, UK presented findings from the phase III TAGS trial, which was conducted to confirm previously reported results of efficacy and tolerability with trifluridine/tipiracil (TAS-102) in pre-treated patients with advanced gastric cancer. TAGS was a global phase III trial that enrolled patients aged ≥18 years with histologically confirmed, non-resectable metastatic gastric cancer ECOG performance status (PS) 0/1, and ≥2 prior chemotherapy regimens. Patients were randomly assigned 2:1 to best supportive care (BSC) plus either TAS-102 at 35 mg/m^2 BID on days 1 to 5 and 8 to 12 of each 28-day cycle (n=337) or placebo (n=170). Sixty-three percent of patients in both treatment arms had received ≥3 lines of prior systemic therapy.

At a median follow-up of 10.7 months median overall survival (OS) was 5.7 months with TAS-102 versus 3.6 months for placebo. TAS-102 provided a 31% reduction in the risk of death, meeting the trial's primary endpoint. The risk of death was lower with TAS-102 compared to placebo (hazard ratio [HR] 0.69; 95% confidence interval [CI], 0.56-0.85; p = 0.0003). The OS analyses favoured TAS-102 over placebo in most of the prespecified subgroups, including ethnicity, geographic region, ECOG PS, and the number of prior treatments.

TAS-102 was associated with a lower risk of disease progression or death compared to placebo (HR 0.57; 95% CI, 0.47-0.70; p < 0.0001). A higher disease control rate of 44% versus 14% (p < 0.0001), and lower risk of ECOG PS deterioration to ≥2 (HR 0.69; 95%, CI 0.56-0.85; p = 0.0005) were also demonstrated with TAS-102 versus placebo. In addition, progression-free survival favoured TAS-102 over placebo across all subgroups.

Grade ≥3 any-cause adverse events (AEs) were reported in 80% of patients on TAS-102/BSC versus 58% of patients on placebo/BSC. Dose delay and dose reduction were required in 195 (58%) patients on TAS 102 due to any cause AEs compared to 37 (22%) placebo-treated patients. Dosing delays were used more often than dose reduction to manage AEs. Each treatment arm reported one death on study. No new safety signals were noted. NCT02500043. Arkenau *et al.* Published simultaneously in the *Lancet Oncology.*[1] Abstract LBA25

Practice point and future research opportunities

In the phase III TAGS study, TAS-102 led to a 31% reduction in the risk of death compared to placebo and statistically significant overall survival prolongation across subgroups, including ECOG PS, in patients with heavily pre-treated metastatic gastric cancer. TAS-102 was also well-tolerated and represents a viable treatment option in this patient population.

Citation:

1. Shitara K, Doi T, Dvorkin M, *et al.* Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncology* 2018; 19(11):1437-1448.

Nivolumab shows long term benefit in previously treated advanced gastric or gastroesophageal junction cancer

Taroh Satoh, Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Osaka, Japan, presented updated data from the phase III ATTRACTION-2 study of nivolumab monotherapy, which had previously demonstrated efficacy in gastric or gastroesophageal junction (G/GEJ) cancer in this study.[1] Professor Satoh and colleagues performed this updated analysis at 2 years after the last patient was enrolled. ATTRACTION-2 enrolled 493 patients with unresectable advanced or recurrent G/GEJ cancer that was refractory to two or more previous chemotherapy regimens. The patients were randomised 2:1 to receive nivolumab monotherapy at 3 mg/kg (n=330) or placebo (n=163) until progressive disease or unacceptable toxicity. The primary endpoint was overall survival (OS).

The median OS with two or more years of follow-up was 5.3 months with nivolumab compared to 4.1 months with placebo (hazard ratio [HR] 0.62; 95% confidence interval [CI], 0.51-0.76). The 12- and 24-month OS rates were 27.3% and 11.6% with nivolumab versus 10.6% and 3.2% with placebo, respectively. A subgroup analysis of data stratified by best objective response showed that patients achieving partial response (PR) on nivolumab had median OS of not reached (NR). In patients with stable disease (SD) on nivolumab versus placebo, the median OS was 9.4 versus 7.6 months (HR 0.70; 95%CI, 0.44-1.09), and median OS in patients experiencing progressive disease (PD) was 3.8 versus 3.8 months (HR 0.86; 95% CI 0.64-1.16), respectively. The 12-month OS rate in patients achieving PR with nivolumab was 86.7%. The 12-month OS rates with nivolumab versus placebo in patients with SD were 36.9% versus 24.2%, and in patients showing PD were 12.4% versus 6.9% respectively. NCT02267343; ONO-4538-12. Satoh *et al.* Abstract 617PD

Practice point and future research opportunities

This 2-year update supports the earlier results published in the *Lancet* of significantly improved overall survival with nivolumab in patients with refractory G/GEJ cancer in the ATTRACTION-2 study.

Citation:

1. Kang YK, Boku N, Satoh T, *et al*. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet* 2017; 390(10111):2461-2471.

Gender-based differences are observed in chemotherapy efficacy and toxicity in oesophagogastric cancer

Michael Davidson, Royal Marsden Hospital NHS Foundation Trust, London, UK discussed gender differences in the metabolism of anti-cancer agents and their impact on the treatment of oesophagogastric cancer. He presented findings from an analysis of pooled data from 1654 patients participating in 4 randomised controlled trials conducted in the UK and Australasia who were treated with first-line chemotherapy for advanced oesophagogastric cancer. The 4 trials had comparable patient populations and used similar standard triplet chemotherapy regimens composed of an anthracycline, platinum, and a fluoropyrimidine. In the pooled dataset, 80.3% of patients were male who predominantly presented with junctional or oesophageal cancers, whereas the 19.7% of female patients had a greater proportion of gastric cancer, 57.4% in women versus 34.1% in men.

The analysis uncovered no significant differences across the trials regarding overall toxicity; all grade or grade ≥3 toxicity was 67.2% in females and 62.8% in males ($p = 0.19$). However, the analysis of individual toxicity results showed quite difference gender-based patterns. Women had significantly higher rates of all grade nausea and vomiting of 89.3% versus 78.3% in men ($p < 0.001$) and grade ≥3 nausea and vomiting of 16.7% versus 9.5%, respectively ($p < 0.001$). All grade diarrhoea rates in women versus men were 53.8% versus 46.9% ($p = 0.027$), stomatitis rates were 49.5% versus 40.7% ($p = 0.004$), and alopecia rates were 81.4% versus 74.3% ($p = 0.009$), respectively. A non-significant trend was observed towards increased rates of grade ≥3 neutropaenia of 45.1% in women versus 40.4% in men and febrile neutropaenia, 11.8 versus 7.7%, respectively. In contrast, all grade peripheral neuropathy occurred more frequently in men than women, the rates were 49.3 % versus 42.6%, respectively ($p = 0.03$). Although the objective response rate was higher at 46.6% in males compared to 40.5% in females, the difference was not statistically significant ($p = 0.051$) and there was no difference in progression-free or overall survival according to sex. Davidson *et al.* Abstract 619PD

Practice point and future research opportunities

This large pooled analysis of the impact of gender on outcome and toxicity in patients treated with equivalent first-line chemotherapy for advanced oesophagogastric cancer shows that women experience significantly higher rates of several toxicities that are primarily gastrointestinal in nature, whereas men had higher rates of peripheral neuropathy. These findings suggest that further research on the impact of the gender on the efficacy and toxicity of chemotherapy and other treatments is necessary. It is known for a long time that there

are differences between males and females in the incidence and prognosis of many non-gender-specific cancers. However, although dissimilarities in the reaction of men and women to treatment had already been observed in a number of past clinical trials, they tended to be written off as a statistical artefact and remained absent from the discussion, because no one could explain why such differences might exist. In the clinic, these trends would have been imperceptible to physicians. The large number of patients included in this analysis allowed statistically significant gender differences in the frequency of several side-effects of chemotherapy to be demonstrated. Not only must we discuss their implications, we also need to understand the underlying reasons.

Going forward, we might consider stratifying patients according to their gender in clinical trials, so as to evaluate the efficacy and tolerance of treatments in each sex from the beginning of drug development. If further studies systematically confirm that women are more prone than men to a wider range of side-effects, then we will also need to think about entirely different prevention and support strategies for these patients.

Citations:

1. Webb A, Cunningham D, Scarffe JH, et al. Randomized Trial Comparing Epirubicin, Cisplatin, and Fluorouracil Versus Fluorouracil, Doxorubicin, and Methotrexate in Advanced Oesophagogastric Cancer. JCO 1997; 15(1):261-267.

2. Ross P, Nicolson M, Cunningham D, et al. Prospective Randomized Trial Comparing Mitomycin, Cisplatin, and Protracted Venous-Infusion Fluorouracil (PVI 5-FU) With Epirubicin, Cisplatin, and PVI 5-FU in Advanced Esophagogastric Cancer. JCO 2002; 20(8)1996-2004.

3. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. NEJM 2008; 358(1):36-46.

4. Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 2013; 14(6):481-489.

Durable anti-tumour activity demonstrated by combined atezolizumab plus bevacizumab in hepatocellular carcinoma

Findings from a phase Ib trial presented by Michael J. Pishvaian, Oncology, Georgetown University, Washington, USA suggested that combining bevacizumab and atezolizumab may have a synergistic effect. Bevacizumab may enhance the activity of atezolizumab by reversing VEGF-mediated immunosuppression to promote T-cell infiltration into the tumour, which may increase the anti-cancer immune response. Dr. Pishvaian and colleagues carried out this multi-arm study of atezolizumab plus bevacizumab in patients with gastric, pancreatic, and oesophageal cancer. The results reported at ESMO 2018 described first-line atezolizumab/bevacizumab treatment compared with atezolizumab alone in patients with unresectable or metastatic hepatocellular carcinoma (HCC). Eligible patients had measurable disease per RECIST v1.1, an ECOG performance status of 0 or 1, adequate haematologic and organ function, and had not received prior systemic therapy. The patients'

median age was 62 years, 57% were from Asian countries other than Japan, and 41% of patients were from either Japan or the United States. The underlying cause of HCC was hepatitis B virus (HBV) infection in 50% of patients, hepatitis C virus (HCV) infection in 29%, and non-viral in 21% of patients. Extrahepatic spread was present in 71% of patients and 53% had macrovascular invasive disease. Previous local treatments included transarterial chemoembolization in 54% of patients, and 36% had radiotherapy. Atezolizumab at 1200 mg plus bevacizumab at 15 mg/kg was administered every 3 weeks to 103 patients. The primary objectives were safety and efficacy based on investigator-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included progression-free survival (PFS) and duration of response (DoR) per RECIST v1.1.

At the clinical data cut-off, 68 patients were evaluable for safety and efficacy. With a minimum of 18 weeks of follow-up, the ORR was 34%, The best response was a complete response (CR) in one (1%) patient, partial responses (PRs) in 22 (32%), and 30 (44%) patients achieved stable disease, for a disease control rate (DCR) of 78%. The DCR at 24 weeks was 50%. The median DoR was not reached (range, 1.6+ to 22.0+ months). Nineteen of 23 confirmed responses were ongoing and these responses lasted ≥6 months in 11 patients. The response rates did not differ by region or baseline characteristics. The ORR by aetiology was 33% HBV, 46% HCV, and 15% for non-viral. The median duration of response was ≥6 months in 52% of responders and ≥12 months in 26%.

The investigator-assessed median PFS was 14.9 (range, 1.0 to 23.9+) months and the 6-month PFS rate was 71%. The median overall survival was not reached (range, 0.8 - 24.0+ months). No new safety signals were identified beyond the established safety profile of the individual agents. Seventeen (25%) patients had treatment-related grade 3/4 adverse events, 12% of which were hypertension. NCT02715531. Pishvaian *et al.* Abstract LBA 26

Practice point and future research opportunities

Treatment options are limited for advanced HCC, representing an unmet need. Due to late appearance of symptoms, more than 80% of patients present with unresectable or advanced HCC. First-line therapy with tyrosine kinase inhibitors has improved survival over placebo; however, responses and durable responses and complete responses are rare.

In July 2018, the US Food and Drug Administration granted atezolizumab a breakthrough therapy designation for use in combination with bevacizumab as a first-line treatment for patients with advanced or unresectable HCC. The combination of the PD-L1 inhibitor atezolizumab and the VEGF inhibitor bevacizumab showed promising and durable anti-tumour activity in this phase Ib study of patients with advanced HCC. Other immune checkpoint inhibitors have shown activity in the first-line treatment of HCC: an ORR of 23% has been reported for first-line nivolumab in a phase I/II study. There is an ongoing phase III trial of atezolizumab plus bevacizumab (IMmotion 151) in renal cell carcinoma that should add to these data.

Novel infigratinib shows promising activity in patients with previously treated advanced cholangiocarcinoma and FGFR2 fusions

Lead author Milind Javie, Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, the University of Texas MD Anderson Cancer Centre in Houston, USA presented findings from one of the first studies to target patients with intrahepatic cholangiocarcinoma. The multicentre, open-label study enrolled 71 patients with fibroblast growth factor receptor 2 (*FGFR2)* fusions, which occur in approximately 13% to 17% of patients with intrahepatic cholangiocarcinoma. The study evaluated the anti-tumour activity of infigratinib, an ATP-competitive FGFR1–3-selective oral tyrosine kinase inhibitor, in patients with previously-treated advanced intrahepatic cholangiocarcinoma and *FGFR2* fusions. Infigratinib was administered at 125 mg orally per day for 21 days of 28-day cycles until unacceptable toxicity, disease progression, investigator discretion, or withdrawal of consent. The primary endpoint was investigator-assessed confirmed overall response rate (cORR) by RECIST v1.1 and secondary endpoints included progression-free survival (PFS), disease control rate (DCR), best overall response (BOR), overall survival (OS), safety, and pharmacokinetics.

At a median follow-up of 8.4 months, patients had been treated for a median of 5.5 months; the ORR was 31.5% (95% confidence interval [CI], 20.5%-43.1%), and the cORR was 26.9% (95% CI, 16.8%-39.1%). In 28 patients receiving ≤1 prior lines of treatment the cORR was 39.3% and cORR was 17.9% in 39 patients who had received ≥2 prior therapies. The DCR was 83.6% (95% CI, 72.5–91.5%), with a median duration of response of 5.4 months. Moreover, the median PFS and OS were 6.8 months (95% CI, 5.8-7.6) and 12.5 months (9.9-16.6), respectively.

At data cut-off, 62 patients had discontinued treatment. The most commonly reported any-grade treatment-emergent adverse events (TEAEs) included hyperphosphatemia (73.2%), fatigue (49.3%), stomatitis (45.1%), alopecia (38.0%), and constipation (35.2%). Grade 3/4 TEAEs occurred in 47 (66.2%) patients and included hypophosphatemia in 14.1%, hyperphosphatemia in 12.7%, and hyponatremia in 11.3% of patients. The authors stated that infigratinib-associated toxicity was manageable. NCT02150967. Javle *et al.* Abstract LBA 28

Practice point and future research opportunities

In general, patients with cholangiocarcinoma receive first-line chemotherapy with gemcitabine or cisplatin; however, there are very few options in the second-line setting. Progression-free survival is usually approximately 3 months with standard therapy, such as capecitabine, 5-fluorouracil or FOLFOX. Unfortunately, these patients have poor outcomes and there are quality-of-life issues with second-line chemotherapy. The selective pan-FGFR kinase infigratinib demonstrated a manageable toxicity profile and clinically meaningful activity following chemotherapy in patients with intrahepatic cholangiocarcinoma according

to updated phase II findings presented at ESMO 2018. These findings merit further study of infigratinib in larger, randomised controlled trials.

GENITOURINARY TUMOURS, NON-PROSTATE

Avelumab plus axitinib doubles response over sunitinib as first-line treatment of advanced renal cell carcinoma

Robert J. Motzer, Memorial Sloan Kettering Cancer Centre in New York, USA presented findings from the JAVELIN Renal 101, which support avelumab plus axitinib as a new standard of care for first-line treatment of patients with advanced renal cell carcinoma (RCC). The phase III JAVELIN Renal 101 trial enrolled 886 patients with advanced or metastatic RCC who were randomly assigned 1:1 to receive 10 mg/kg of avelumab intravenously every 2 weeks plus 5 mg of oral axitinib twice daily in 6-week cycles or 50 mg of oral sunitinib once daily for a 4-weeks-on/2-weeks-off schedule; 442 patients were treated with the combination while 444 received sunitinib. Overall, 560 (63.2%) patients were PD-L1–positive; of these, 270 patients received the combination and 290 patients received sunitinib. Patients with good- (21%), intermediate- (62%), and poor-risk disease (16%) according to the Memorial Sloan Kettering Cancer Centre (MSKCC)/Motzer Criteria were included. Progression-free survival (PFS) by blinded independent central review (BICR) and overall survival (OS) in the PD-L1–positive group were the primary endpoints. PFS and OS in the overall population irrespective of PD-L1 status, objective response rate (ORR), and safety served as the secondary endpoints.

The PD-L1–positive cohort showed median PFS of 13.8 months (95% confidence interval [CI], 11.1-not estimated [NE]) with avelumab/axitinib compared to 7.2 months (95% CI, 5.7-9.7) with sunitinib, representing a 39% reduction in the risk of disease progression or death (hazard ratio [HR] 0.61; 95% CI, 0.475-0.790; $p < 0.0001$). The ORR with the combination was twice that of sunitinib; with the avelumab plus axitinib combination, the ORR was 55.2% (95% CI, 49.0-61.2) compared to 25.5% (95% CI, 20.6-30.9) with sunitinib. The combination arm ORR included 4 complete responses (CRs), 51 partial responses (PRs), 27 patients achieved stable disease (SD), and 11 patients receiving the combination showed progressive disease (PD).

In the overall population, the median PFS with combined avelumab and axitinib versus sunitinib was 13.8 months (95% CI, 11.1-NE) versus 8.4 months (95% CI, 6.9-11.1), respectively (HR 0.69; 95% CI, 0.563 - 0.840; $p = 0.0001$). Moreover, the ORR with avelumab/axitinib was 51.4% (95% CI, 46.6-56.1) versus 25.7% (95% CI, 21.7-30.0) with sunitinib. With the combination, the ORR included 3 CRs, 48 PRs, 30 SD, and 12 patients had PD. In the PD-L1–positive and overall population arms, 73% and 70% of patients remained on avelumab/axitinib treatment, respectively, versus 65% and 71% of those on sunitinib. Median duration of response was not reached in either treatment arm in either population. The OS data are not yet mature.

The combination also elicited a favourable safety profile; 51 (4%) patients on the combination arm and 48 (7%) patients on the sunitinib arm experienced grade 3/4 treatment-related adverse events (TRAEs), the most common being diarrhoea in 5% versus 3% of

patients, respectively. All-grade TRAEs were similar between arms. Four percent of TRAEs led to avelumab/axitinib discontinuation versus 8% with sunitinib, Grade ≥3 TRAEs were reported in 71.2% of patients in the combination arm versus 71.5% of patients in the sunitinib arm, and led to treatment discontinuation in 22.8% versus 13.4%, respectively. One patient on avelumab/axitinib died due to a TRAE. The rationale for this trial emerged from a phase Ib trial, wherein avelumab plus axitinib demonstrated encouraging anti-tumour activity in patients with advanced RCC. NCT02684006. Motzer *et al.* Abstract LBA6

Practice point and future research opportunities

JAVELIN Renal 101 is the first positive phase III study of an immune checkpoint blocker, avelumab, combined with a tyrosine kinase inhibitor (TKI), axitinib, compared to the TKI, sunitinib, in the first line treatment of advanced RCC. TKIs have been the mainstay of treatment; however, TKIs and checkpoint blockers may both have potential immune-modulating functions that, when combined, may provide clinical benefit that exceeds the effects of the respective drugs alone, without compromising toxicity. The response rates with this combination were twice as good as previous standards of care, and PFS is entering into very impressive territory for a randomised trial. Avelumab/axitinib benefit was observed regardless of risk group and regardless of PD-L1 status; it may be that testing for PD-L1 is not necessary to choose patients for this therapy.

Citation:

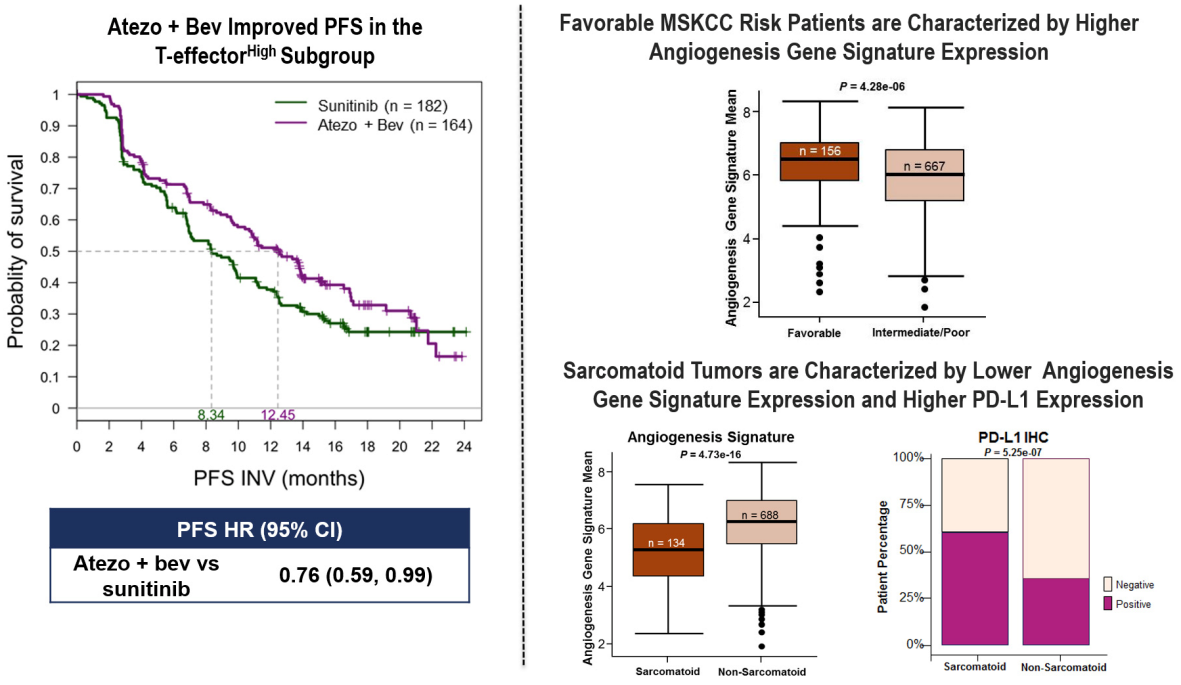
1. Coueiri TC, Larkin J, Oya M, et al. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear clell renal-cell carcinoma (JAVELINE Renal 100): an open-label, dose finding and dose-expansion, phase 1b trial. Lancet Oncol 2018; 19:451-60.

The molecular characteristics of clinical response to atezolizumab plus bevacizumab differ from sunitinib in metastatic renal cell carcinoma

Brian I. Rini of the Department of Solid Tumour Oncology, Taussig Cancer Institute Cleveland Clinic in Cleveland, United States of America presented results from the IMmotion151 phase III study that confirmed previous findings of improved progression-free survival (PFS) with combined atezolizumab/bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (mRCC). Dr. Rini and colleagues conducted the IMmotion151 trial to confirm the PFS findings in patients whose tumours express PD-L1 and also to correlate molecular gene expression signatures with clinical outcomes, prognostic risk groups, and tumour histology. The investigators noted that biomarker analyses performed in a phase II study (IMmotion150) suggested that T effector (T_{eff}) and interferon gamma, as well as angiogenesis gene expression signatures (GEs) were associated with differential outcomes to atezolizumab plus bevacizumab and sunitinib. Therefore, they performed prespecified genomic analyses to validate these GEs and to determine their association with clinical outcomes from 823 patients in IMmotion151, and they also evaluated the association of GEs with Memorial Sloan Kettering Cancer Centre (MSKCC) risk groups, and sarcomatoid histology.

The IMmotion151 study met the co-primary endpoint of improved PFS (Figure) with atezolizumab plus bevacizumab over sunitinib in PD-L1-positive patients across all MSKCC risk groups (hazard ratio [HR] 0.74; 95% confidence interval [CI], 0.57-0.96; p = 0.02). Improved PFS was also observed in patients with sarcomatoid histology (HR 0.56; 95% CI, 0.38-0.83).

Different patterns of molecular correlates to clinical outcomes associated with the atezolizumab/bevacizumab response versus sunitinib. Tumour molecular analyses showed that high T_{eff} GE was associated with PD-L1 expression, as evaluated by immunohistochemistry. High T_{eff} GE also associated with longer PFS for atezolizumab plus bevacizumab compared to sunitinib (HR 0.76; 95% CI, 0.59-0.99). In patients receiving sunitinib, high angiogenesis GE was associated with improved PFS (HR 0.59, 95% CI, 0.47-0.75); however high angiogenesis GE did not differentiate between atezolizumab plus bevacizumab versus sunitinib clinical activity (HR 0.95; 95% CI, 0.75-1.19). Atezolizumab plus bevacizumab improved PFS versus sunitinib in the subset of patients with low angiogenesis GE (HR 0.68; 95% CI, 0.52-0.89). Angiogenesis GE was found to be higher in favourable versus intermediate to poor MSKCC risk groups (p = 4.28^{e-06}). PD-L1 prevalence was higher (63%) in sarcomatoid tumours, compared to 39% in non-sarcomatoid tumours. Angiogenesis GE was lower in sarcomatoid compared to non-sarcomatoid tumours (p = 4.73^{e-16}). NCT02420821. Rini *et al.* Abstract LBA31



Practice point and future research opportunities

The IMmotion 151 trial confirmed previous PFS findings with atezolizumab plus bevacizumab. In addition, the study provided a prospective evaluation of biomarkers and validated molecular signatures that could differentiate between clinical outcomes to the combination of VEGF inhibition provided by bevacizumab and PD-L1 inhibition provided by atezolizumab compared to sunitinib in first-line treatment of patients with mRCC. These data also identified tumour genomic profiles that associated with prognostic risk groups and sarcomatoid histology. The biomarker findings from IMmotion151 advance the understanding of the biology of kidney cancer and may be used to inform future strategies enabling personalised therapy in patients with mRCC.

Adjuvant axitinib shows no advantage over placebo in patients at risk of recurrent renal cell carcinoma

Marine Gross-Goupil, Department of Oncology, CHU Bordeaux Hopital St. André, Bordeaux, France and colleagues evaluated the efficacy and safety of adjuvant axitinib compared to placebo as adjuvant treatment in patients at high risk of renal cell carcinoma (RCC) recurrence. Axitinib is currently approved for second-line treatment of advanced RCC, but efficacy as an adjuvant therapy was untested, to date. The investigators conducted the phase III, randomised, double-blind ATLAS trial in patients who had undergone nephrectomy for >50% clear-cell RCC. At randomisation, patients had no evidence of macroscopic residual or metastatic disease per independent review committee (IRC) confirmation. The intent-to-treat (ITT) population comprised all 724 randomised patients ≥pT2 and/or N1 with any Fuhrman grade (FG) and ECOG performance status 0-1. Patients were stratified by risk group and country and randomised to receive oral axitinib at 5 mg twice daily (n=363) or placebo (n=361) for a minimum of one year up to 3 years, until recurrence, evidence of a second primary malignancy, significant toxicity, or consent withdrawal. Maximum dose increases to 10 mg and decreases to 1 mg twice daily were allowed. The majority (73.3%) of patients were Asian, with a median age of 58.0 years, and 56.5% of patients were at highest recurrence risk, defined as pT3 with FG ≥3 or pT4 and/or N1 with any FG. The primary endpoint was disease-free survival (DFS) per IRC, and secondary endpoints included overall survival (OS) and safety.

After a pre-planned interim analysis at 203 DFS events the trial was halted due to futility. Median DFS per IRC in the ITT population was identical at not reached (NR) in the axitinib and placebo arms; median DFS was NR (95% confidence interval [CI], 4.1-NR) in both arms (hazard ratio [HR] 0.890; p = 0.3211). Median DFS per IRC in the highest risk cohorts was NR (95% CI, 3.5-NR) in 209 patients on axitinib versus NR (95% CI, 2.5-NR) in 209 patients on placebo (HR 0.0704; p = 0.0704). In the lowest risk cohort, median DFS was NR (95% CI, NR-NR) versus NR (95% CI, NR-NR) with the respective treatments (HR 1.016; p = 0.9483). The DFS results per investigator assessment in the ITT and low risk populations were also similar. However, in the high-risk cohort, median DFS was 4.4 months (95% CI, 3.4-NR) with axitinib compared to 2.8 (95% CI, 1.5-NR) with placebo (HR 0.641; 95% CI,

0.468-0.879; p = 0.0051). At data cut-off, 7.7% of axitinib-treated patients and 7.2% of patients on placebo had died. The OS data were not mature. The median treatment duration was 19.9 (range, 0.1 to 37.0) months with axitinib versus 21.9 (range, 0.0 to 36.9) months with placebo.

Patients receiving axitinib reported more adverse events (AEs) compared to placebo, 98.6% versus 92.5%, respectively. The most common AE was hypertension, which was reported in 64.3% and 24.5% of the respective arms. Serious AEs were reported in 19.4% versus 14.5%, and grade 3-4 AEs occurred in 61.2% versus 30.1% of the respective treatment arms. Dose reductions were more common with axitinib at 60.4% versus 13.4% with placebo, as were dose interruptions at 67.4% versus 34.8%, respectively. Treatment discontinuation due to AEs was reported for 23.3% of axitinib patients compared to 11.1% of placebo patients. NCT01599754. Gross-Goupil *et al.* Published simultaneously in the *Annals of Oncology.*[1] Abstract 863O

Practice point and future research opportunities

In ATLAS, no significant differences in DFS per IRC were observed with axitinib and placebo in the ITT or in risk subgroups. Although investigator assessed DFS also demonstrated similar results for both treatments in the ITT and low risk population, a significant difference for DFS per investigator was reported in the highest risk cohort. No new safety signals were seen with axitinib in patients at high risk of recurrent RCC.

Citation:

1. Gross-Goupil M, Kwon TG, Eto M, *et al.* Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. Annals of Oncology 2018; 29(12):2371-2378.

Neoadjuvant pembrolizumab plus cisplatin and gemcitabine shows promise in locally advanced urothelial cancer

Lead author Christopher J. Hoimes, Medical Oncology, Case Western Reserve University School of Medicine/University Hospitals Seidman Cancer Centre, Cleveland, USA and colleagues investigated whether pembrolizumab, which is approved by both the FDA and EMA for the treatment of metastatic urothelial cancer, could improve response rates in the locally advanced setting when combined with gemcitabine and cisplatin neoadjuvant chemotherapy (NAC). He presented findings from cohort I of this multicentre phase Ib/II chemo-immunomodulation trial of pembrolizumab plus NAC comprised of gemcitabine and cisplatin. This combination was administered as neoadjuvant therapy in chemotherapy-eligible patients with cT2-4aN0M0 urothelial cancer or mixed histology. In phases Ib and II, patients received the same treatment of pembrolizumab at 200 mg every 3 weeks on day 8 for 5 doses, cisplatin at 70 mg/m^2 on day 1, and gemcitabine at 1000 mg/m^2 on days 1 and 8 of a 21 day cycle for 4 cycles, followed by radical cystectomy with node dissection (RC). The safety analysis required that patients had received one dose of pembrolizumab and the

efficacy evaluation required that patients had received two doses of pembrolizumab plus RC. The primary endpoint in this ongoing study is a pathologic non-muscle invasive rate (PaIR, ≤pT1N0M0) of ≥48%.

At ESMO 2018, findings from 40 evaluable patients were presented. The median age of the patients was 65 years, 75% were male, 10% had mixed urothelial cancer histology, and 52% of patients had a PD-L1 combined positive score ≥10. Baseline stage was cT2 in 51% of patients, cT3 in 44%, and cT4a in 5% of patients. During phase I, no dose limiting toxicities (DLTs) occurred in the 6 patients on phase Ib; however, one death occurred on day 9 post-RC due to mesenteric ischemia (ileal conduit). One patient did not undergo RC due to an adverse event (AE) of grade 4 thrombocytopenic purpura. One patient with presumed grade 3 myocardial infarction during cycle 4 had a negative inpatient cardiac workup but completed therapy and RC without experiencing further grades 3/4 AEs. One grade 4 and ten grade 3 hyponatremia events occurred but did not prevent RC. The hyponatremia events included 2-each of thromboembolism, elevated creatinine, and hyponatremia and 1-each of dehydration, emesis, neutropenic fever, and infection. Grade 3/4 cytopenias occurred in 57% of patients.

A median of 5 doses of pembrolizumab was administered, as well as a median of 4 cisplatin doses, and 8 gemcitabine doses. Four patients refused RC and one patient did not have RC due to an AE; in the remaining patients, the median time to surgery was 18.5 weeks from registration, and 5.3 weeks from last dose. The PaIR was 60% (95% confidence interval [CI], 42-74). The PaIR did not show an association with the baseline PD-L1 score. At a median follow-up of 14 months (range, 1.6 to 33.3) the estimated 12-month relapse free-survival was 80%, overall survival was 94%, and disease specific survival was 97%. NCT02365766. Hoimes *et al.* Abstract LBA 33

Practice point and future research opportunities

In this study, neoadjuvant cisplatin and gemcitabine plus pembrolizumab administered as adjuvant therapy in locally advanced urothelial cancer demonstrate manageable toxicity, and the time to surgery was comparable to that reported for NAC. Pembrolizumab in combination with cisplatin and gemcitabine associated with robust disease downstage and a control rate that warrants further study.

Encouraging responses observed with pembrolizumab in high-risk non–muscle invasive bladder cancer that is unresponsive to Bacillus Calmette-Guérin therapy

Ronald de Wit, Erasmus MC Cancer Institute in Rotterdam, Netherlands explained that pembrolizumab may prevent activation of the PD-1 pathway that has been implicated in patients with bladder cancer who become resistant to Bacillus Calmette-Guérin (BCG) therapy. Pembrolizumab has also demonstrated significant activity in patients with metastatic urothelial carcinoma, prompting the single-arm, open-label, phase II KEYNOTE-

057 trial. This trial evaluated the efficacy and safety of pembrolizumab in patients with high risk, BCG-unresponsive non–muscle invasive bladder cancer (NMIBC).

Professor de Wit presented preliminary results for cohort A, which contained 130 patients with histologically confirmed high-grade BCG-unresponsive NMIBC, including carcinoma in situ (CIS) alone or with a combination of CIS and papillary disease. All patients had been treated with adequate BCG therapy and were unable or unwilling to undergo radical cystectomy. Patients received pembrolizumab at 200 mg fixed dose intravenously every three weeks until recurrence, disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. The primary endpoint for cohort A was complete response (CR); key secondary end points were safety and duration of response (DoR).

Patients found to have progressive disease during treatment were required to discontinue. At a median follow-up of 9.4 (range, 0.2 to 21.2) months, 101 patients remained. At the third month, 31 patients achieved CR by central assessment for a CR rate of 36.5% (95% confidence interval [CI], 26.3-47.6). In responding patients, 85.6% of these responses were maintained after 6 months; the median DoR was 8.1 (range, 0+ to 13.7+) months. Treatment-related adverse events (AEs) occurred in 54 (55.7%) patients. The most commonly reported AEs in ≥5% of patients included diarrhoea (9.3%), pruritus (9.3%), fatigue (7.2%), hypothyroidism (5.2%), maculopapular rash (5.2%), and arthralgia (5.2%). Treatment-related grade 3-5 AEs occurred in 11 (11.3%) patients. Immune-mediated AEs were seen in 15 (15.5%) patients and were grade 3/4 in 2 (2.1%) patients. One death occurred on study that was considered treatment related. The KEYNOTE-057 trial is ongoing. NCT02625961. De Wit *et al.* Abstract 864O

Practice point and future research opportunities

Approximately 40% of patients with high-risk NMIBC progress to muscle-invasive disease. Treatment options for high-risk NMIBC have historically been limited, with many patients relying on radical cystectomy as their only option following disease recurrence. In the KEYNOTE-057 trial, pembrolizumab demonstrated encouraging anti-tumour activity in patients with high-risk, BCG-unresponsive NMIBC with CIS. The safety profile of pembrolizumab in this population is consistent with that of previous studies.

Adding ipilimumab improves nivolumab response in PD-L1 unselected patients with platinum pre-treated metastatic urothelial cancer

Findings from the CheckMate 032 study were presented by lead author Jonathan E. Rosenberg of the Department of Medicine at Memorial Sloan-Kettering Cancer Centre in New York, USA. CheckMate 032 was a multicentre, open-label study that enrolled patients with previously treated locally advanced or metastatic urothelial cancer (mUC), RECIST v1.1 measurable disease, and ECOG performance status ≤1; most patients had been heavily pre-treated. The study evaluated nivolumab monotherapy and 2 dose levels of combined nivolumab and ipilimumab. Seventy-eight patients received nivolumab

monotherapy at 3 mg/kg, 104 received nivolumab at 3 mg/kg plus 1 mg/kg ipilimumab for up to 4 doses followed by nivolumab 3 mg/kg, and 92 patients received 1 mg/kg nivolumab plus 3 mg/kg ipilimumab for up to 4 doses followed by nivolumab 3 mg/kg. The primary endpoint in CheckMate 032 was investigator-assessed objective response rate (ORR) per RECIST v1.1 with duration of response (DoR). Secondary endpoints included investigator-assessed progression-free survival (PFS), overall survival (OS), and safety.

Although some patients with platinum-pretreated mUC demonstrated good responses to nivolumab monotherapy, the response rate and survival were higher with combined nivolumab plus ipilimumab therapy. The minimum follow-up was 37.7 months with nivolumab monotherapy, 38.8 months for the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg arm, and 7.9 months for the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort. The ORR per investigator (Table) was 26% (95% confidence interval [CI], 16-37%), 27% (95% CI, 19-37%), and 38% (95% CI, 28-49%), with the respective treatments. The median DoR was 30.5 (95% CI, 8.3–not estimable [NE]), 22.3 (95% CI, 12.8-NE), and 22.9 (95% CI, 9.8-NE) months, respectively. Median PFS was 2.8 (95% CI, 1.5-5.3) with nivolumab monotherapy, 2.6 (95% CI, 1.4-3.9) with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, and 4.9 (95% CI, 2.7-6.6) months with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; median OS was 9.9 (95% CI, 7.3-21.1), 7.4 (95% CI, 5.6-11.0), and 15.3 (95% CI, 10.1-27.6) months, respectively.

The response was highest in patients with tumour cell expression of PD-L1 ≥1%, especially at the nivolumab 1 mg/kg / ipilimumab 3 mg/kg dose. The ORR in patients with PD-L1 ≥1% was 27% (95% CI, 12–48%) with nivolumab, 35% (95% CI, 19–55%) nivolumab 3 mg/kg / ipilimumab 1 mg/kg, and 58% (95% CI, 39–76%) with nivolumab 1 mg/kg / ipilimumab 3 mg/kg. By contrast, patients with PD-L1 < 1% demonstrated an ORR of 26% (95% CI, 14–41%), 25% (95% CI, 14 – 38%), and 24% (95% CI, 12–40%) with the respective treatments.

Table: Best overall response per investigator.

Characteristic	NIVO3 (N = 78)	NIVO3IPI1 (N = 104)	NIVO1IPI3 (N = 92)
Confirmed ORR, %	25.6	26.9	38.0
95% CI	16.4–36.8	18.7–36.5	28.1–48.8
Best overall response, n (%)			
Complete response	8 (10)	8 (8)	6 (7)
Partial response	12 (15)	20 (19)	29 (32)
Stable disease	21 (27)	24 (23)	23 (25)
Progressive disease	30 (38)	44 (42)	20 (22)
Unable to determine	7 (9)	8 (8)	12 (13)
Not reported	0	0	2 (2)

In the overall patient population, grades 3/4 treatment-related adverse events (TRAEs) occurred in 27%, 31%, and 39% of patients in the respective treatment arms. Grade 5 TRAEs of pneumonitis were reported in one patient in the nivolumab monotherapy arm and one patient in the nivolumab 3 mg/kg / ipilimumab 1 mg/kg arm. NCT01928394. Rosenberg *et al.* Abstract LBA32

Practice point and future research opportunities

CheckMate 032 is a multicentre, phase I/II study and not a randomised trial. It cannot compare across studies and cannot even compare investigator and BICR results. The findings reproduce previous results in urothelial cancer, but a phase III trial is needed and ongoing (CheckMate 901; NCT03036098). Selected toxicities are higher but don't preclude treatment. The response rate of 38% is encouraging. The follow-up in CheckMate 031 is not mature but long-term outcomes may be important. PD-L1 positive tumours may benefit; however, the utility of PD-L1 as a good biomarker remains unresolved. More detailed interrogation of tumours beyond PD-L1 would be ideal.

Cabozantinib improves survival compared with everolimus or sunitinib in PD-L1 unselected patients with metastatic renal cell carcinoma

Toni K. Choueiri, Division Of Genitourinary Medical Oncology, Dana-Farber Cancer Institute in Boston, USA presented findings from an analysis of 2 randomised controlled trials that demonstrated cabozantinib improved progression-free survival (PFS) and overall survival (OS) consistently over everolimus and sunitinib in patients with metastatic, clear cell, renal cell carcinoma (mRCC). Dr. Choueiri and Dr. Sabina Signoretti, the senior author of the research, also investigated the utility of PD-L1 status assessed by immunohistochemistry of samples from the trials as a potential prognostic and/or predictive biomarker of cabozantinib activity in mRCC. According to data from the CheckMate 214 study, PD-L1 expression on tumour cells was associated with improved outcomes in patients receiving nivolumab and ipilimumab compared to sunitinib.[1] Furthermore, prior studies from Drs. Choueiri and Signoretti showed that PD-L1 expression is associated with worse outcomes to sunitinib in mRCC patients.[2] Cabozantinib is an oral kinase inhibitor that is an option for first- and second-line treatment of patients with mRCC, based upon anti-tumour activity demonstrated in the CABOSUN and METEOR randomised clinical trials.

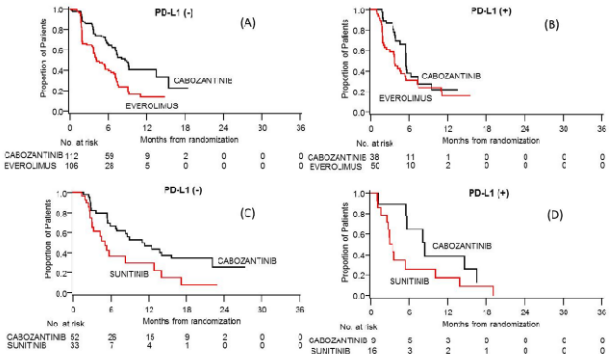
Using formalin-fixed paraffin-embedded baseline tumour tissue obtained from 110 patients participating in CABOSUN and 306 patients from METEOR, the investigators assessed PD-L1 expression in both tumour cells and immune cells by performing immunohistochemical (IHC) double-staining for PD-L1 and the immune cell markers, CD45/CD163. The percentages of PD-L1-positive tumour or immune cells were assessed by image analysis. Comparison of the overall response rate (ORR) by RECIST between PD-L1-positive, using ≥1% as cut-off, versus PD-L1-negative tumours was done by Fisher's exact test. Cox regression was used to correlate PFS and OS with tumour PD-L1 expression across each treatment arm. The ORR, PFS and OS were per independent central review (ICR).

Cabozantinib was associated with improved PFS and OS versus everolimus or sunitinib that was irrespective of PD-L1 expression. With cabozantinib versus everolimus treatment in METEOR, the median PFS per IRC was 8.5 versus 5.6 months (p = 0.027), and median OS was 21.3 versus 15.1 months, p = 0.003, respectively. Median PFS per IRC with cabozantinib versus sunitinib in CABOSUN was 8.3 versus 5.5 months (p = 0.059) and median OS was 28.1 versus 20.8 months (p = 0.05). Twenty-nine percent of METEOR and 23% of CABOSUN samples contained PD-L1-positive tumour cells. Treatment comparison of PFS according to PD-L1 expression revealed consistent results across PD-L1 measures that included immune cell PD-L1 expression, combined PD-L1 score, and the use of different PD-L1 cut-offs.

By univariate analysis, patients with PD-L1 levels < 1% on tumour cells had better PFS and OS than patients with PD-L1-positive tumour cells in both trials independent of therapy. Median PFS with cabozantinib versus everolimus in patients with tumour cell PD-L1 expression < 1% was 8.5 (95% confidence interval [CI], 7.2-13.5) versus 4.1 (95% CI, 3.7-6.0) months (hazard ratio [HR] 0.46; 95% CI, 0.32-0.66). Median PFS with cabozantinib versus everolimus in patients with PD-L1 expression ≥ 1% was 5.6 (95% CI, 4.5-7.4) versus 3.7 (95% CI, 2.5-5.3) months (HR 0.66; 95% CI, 0.40-1.11), respectively.

In the CABOSUN trial, median PFS (Figure) with cabozantinib versus sunitinib in patients with PD-L1 expression < 1% was 11.0 (95% CI, 6.8-15.6) versus 5.0 (95% CI, 3.0-12.9) months (HR 0.47; 95% CI, 0.26-0.86). Median PFS with the respective treatments in patients with PD-L1 expression ≥ 1% was 8.4 (95% CI 1.1-16.6) versus 3.1 (95% CI, 1.6-10.1) months (HR 0.46; 95% CI, 0.18-1.21). Although differences between treatment arms were not statistically significant in multivariable analyses adjusting for International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk groups and bone metastasis, in either trial, these data support use of cabozantinib in a PD-L1 unselected population. CABOSUN: Alliance A031203 and NCT01865747. METEOR: NCT01835158. Choueiri et al. Abstract LBA34

Cabozantinib is associated with improved PFS and OS compared to everolimus and sunitinib irrespective of PD-L1 expression.



	METEOR (N=306)					CABOSUN (N=110)				
	CABOZANTINIB (C)		EVEROLIMUS (E)		C vs E	CABOZANTINIB (C)		SUNITINIB (S)		C vs S
	N	Median Months (95%CI)	N	Median Months (95%CI)	HR (95%CI)	N	Median Months (95%CI)	N	Median Months (95%CI)	HR (95%CI)
PFS										
PD-L1(-)	112	8.5 (7.2-13.5)	106	4.1 (3.7-6)	**0.46 (0.32-0.66)**	52	11.0 (6.8-15.6)	33	5.0 (3-12.9)	**0.47 (0.26-0.86)**
PD-L1(+)	38	5.6 (4.5-7.4)	50	3.7 (2-5.3)	**0.66 (0.40-1.11)**	9	8.4 (1.1-16.6)	16	3.1 (1.6-10.1)	**0.46 (0.18-1.21)**
P-interaction					***0.217***					***0.998***
OS										
PD-L1(-)	112	NR	106	18.4 (15.1-NR)	**0.58 (0.38-0.88)**	52	30.3 (18.8-NR)	33	22.4 (7.6-NR)	**0.71 (0.39-1.29)**
PD-L1(+)	38	18.4 (10.4-22)	50	13.9 (8.7-18.9)	**0.82 (0.47-1.41)**	9	18.1 (1.1-35)	16	21.0 (6.4-30.8)	**0.85 (0.31-2.31)**
P-interaction					**0.359**					**0.372**

Figure. Kaplan Meier estimates of PFS according to treatment, sub-grouped by PD-L1 status in tumor cells in METEOR cohort (A,B); and in CABOSUN cohort (C,D).

© Toni K. Choueiri

Practice point and future research opportunities

In univariate analysis, patients with positive PD-L1 expression in tumour cells had poorer PFS and OS. However, the association between PD-L1 expression on tumour cells and OS was statistically significant in the multivariable analysis combining both trials. Cabozantinib had superior clinical efficacy compared to both everolimus and sunitinib, in both PD-L1 positive and PD-L1 negative patients.

Dual-IHC staining is a robust and efficient technique to characterise PD-L1 status on tumour and immune cells. These data support use of cabozantinib in a PD-L1 unselected population and, possibly, in combination with checkpoint blockers irrespective of PD-L1 status.

Citations:

1. Motzer RJ, ESMO 2017 Presidential session; Motzer RJ, Tannir NM, Mc Dermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018; 378:1277-1290.

2. Choueiri TK, Figueroa DJ, Fay AP, et al. Correlation of PD-L1 tumor expression and treatment outcomes in patients with renal cell carcinoma receiving sunitinib or pazopanib: results from COMPARZ, a randomized controlled trial. Clin Cancer Res 2015; 21(5):1071-7.

GENITOURINARY TUMOURS, PROSTATE

Abiraterone acetate plus prednisone/prednisolone improves survival over androgen deprivation therapy in high- and low-risk metastatic hormone sensitive prostate cancer

Alex P. Hoyle, Uro-Oncology, The Christie NHS Foundation Trust, Manchester, UK pointed out that abiraterone acetate plus prednisone/prednisolone (AAP) is licenced in the European Union for the treatment of high-risk newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC). Licencing was based on results from the LATTITUDE trial but contrary findings came from the STAMPEDE showing similar benefits in M0 and M1 patients, prompting this evaluation of the heterogeneity of the AAP effect on overall survival (OS) and failure-free survival (FFS). The patients had LATITUDE-defined high- and low-risk M1 disease and had been randomised within the STAMPEDE trial to receive androgen deprivation therapy (ADT) or ADT plus AAP. This analysis included centrally reviewed staging scans for M1 patients randomised to ADT (arm A) or AAP (arm G) within STAMPEDE. Following this review, patients were classified as low- or high-risk according to LATITUDE criteria. The primary study endpoint was OS and the secondary endpoint was FFS. Additional exploratory analysis evaluated skeletal related events (SRE), progression-free survival (PFS), and prostate cancer specific survival (PCSS). Secondary differential analysis by tumour volume (high versus low) was done using the criteria defined in the CHAARTED trial.[1]

Out of 990 M1 patients, 901 had evaluable data. Their median age was 67 years and the median prostate specific antigen (PSA) was 96 ng/ml. Of these patients, 473 were high-risk and 428 were low-risk according to LATITUDE criteria. After a median follow-up of 42 months, AAP treated patients demonstrated clinically statistically significant OS improvements in both high-risk patients (hazard ratio [HR] 0.54, 95% confidence interval [CI], 0.41-0.70; $p < 0.001$) and in patients with low-risk (HR 0.66, 95% CI, 0.44-0.98; $p = 0.041$). Patients treated with AAP also showed prolonged FFS within both high- (HR 0.31; 95% CI, 0.25-0.39; $p < 0.001$) and low-risk groups (HR 0.238; 95% CI, 0.17-0.33; $p < 0.001$). No evidence of heterogeneity between risk groups was found in OS or FFS (interaction p-value, $p = 0.385$; $p = 0.294$, respectively). The analyses incorporating the alternative CHAARTED volume definition also displayed similar outcomes. NCT00268476. Hoyle *et al.* Abstract LBA4

Practice point and future research opportunities

This study adds clarity to the disparity between findings from the LATTITUDE and STAMPEDE clinical trials. The OS and FFS were significantly improved in men with primary mHSPC treated with AAP plus ADT compared to men receiving ADT alone, irrespective of risk/volume sub-classification. These results show a treatment benefit with AAP across all mHSPC patients, irrespective of M1 risk/volume sub-stratification using conventional imaging.

Citation:

1. Kyriakopoulos CE, Chen Y-H, Carducci MA, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. JCO 2018; 36(11):1080-1087.

Radiotherapy to the primary tumour improves survival in men with newly diagnosed metastatic prostate cancer and low burden of disease

Chris Parker, Institute for Clinical Research, the Royal Marsden NHS Foundation Trust in Sutton, UK reported results from the multi-arm, multi-stage STAMPEDE study on behalf of the STAMPEDE investigators. This trial included a randomised phase III comparison to test whether radiotherapy to the prostate could enhance local control, slow progression of metastatic disease, and improve overall survival (OS) in men with newly diagnosed metastatic prostate cancer. The study included 2061 men from the UK and Switzerland. The treatment cohorts were well balanced; the median age was 68 years, median PSA was 97 ng/ml, 18% of patients had received early docetaxel, and the metastatic burden was low in 40% of patients, higher in 54%, and unknown in 6% of the men. They were randomly assigned to receive to standard of care (SoC) treatment of androgen deprivation therapy (ADT), or to SoC plus radiotherapy to the prostate, administered at 55Gy/20f daily over 4 weeks or 36Gy/6f weekly over 6 weeks. From 2016 onwards, early docetaxel treatment was allowed.

Radiotherapy to the prostate was found to improve failure-free survival (hazard ratio [HR] 0.68; 95% confidence interval [CI], 0.68-0.84) over ADT. However, OS was not improved with additional radiotherapy compared to ADT (HR 0.92, 95% CI, 0.80-1.06) in the overall population. In prespecified subgroup analysis, OS was improved by radiotherapy to the prostate in patients with low but not high burden of metastatic disease. Radiotherapy improved OS by 32% in 819 men having a low burden of metastatic disease (HR 0.68; 95% CI, 0.52-0.90). In contrast, OS was not prolonged with radiotherapy compared to ADT in 1120 men with higher metastatic burden, which was defined as 4 or more bone metastases with at least one outside the axial skeleton and/or visceral metastases.[2]

Radiotherapy to the prostate was well tolerated with 5% of patients having grade 3/4 adverse events during treatment and 4% following treatment. Radiotherapy to the prostate did not improve survival for unselected patients with newly diagnosed metastatic prostate cancer, but, in a pre-planned analysis, did improve survival in men with a lower metastatic burden. Therefore, prostate radiotherapy should be a standard treatment option for men with oligometastatic disease. NCT00268476. Parker *et al.* Published simultaneously in the *Lancet.*[3] Abstract LBA5_PR

Practice point and future research opportunities

Although outcomes have improved, men still typically die from metastatic prostate cancer within approximately 5 years, so there is a need for more effective treatment. For the first

time, this study provides evidence that treating the local primary tumour is associated with improvement in OS in men with metastatic prostate cancer and minimal disseminated disease. There was no significant increase in overall survival in men with higher burden of disease, which was in line with the previously reported HORRAD trial.[2] A limitation of this study it that even though it was a large, randomised phase III trial, only 18% of the patients had received early docetaxel and none had received early abiraterone, although these treatments are now part of standard treatment in fit men.

For men with newly diagnosed oligometastatic prostate cancer and lower disease burden, it is quite likely that these data are practice changing; however, for men with higher burden of disease more data are needed regarding whether upfront local treatment improves or prevents local symptoms, which, by itself, may justify its use in the absence of an OS benefit.

Citations:

1. Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. NEJM 2015; 373: 737-746.

2. Boevé L, Hulshof M, Vis A, et al. PD10-10 a prospective, randomized controlled trial evaluating overall survival in patients with primary bone metastatic prostate cancer (MPCA) receiving either androgen deprivation therapy (ADT) or ADT combined with concurrent radiation therapy to the prostate, final data from the HORRAD trial. The Journal of Urology 2018; 199:e231-e232.

3. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018; 392(10162):2353-2366.

GYNAECOLOGICAL CANCERS

Olaparib maintenance significantly prolongs PFS in patients with newly diagnosed BRCA1/2 mutated advanced ovarian cancer

Kathleen Moore, Stephenson Cancer Centre, University of Oklahoma in Norman, USA presented findings from the ongoing SOLO-1 study, which is the first phase III, randomised, placebo-controlled trial evaluating maintenance with the PARP inhibitor, olaparib, in patients with a *BRCA1/2* mutation who had received platinum-based chemotherapy for newly diagnosed advanced ovarian cancer. Enrolled patients had FIGO stage III-IV, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer with germline or somatic *BRCA* mutations. Patients were required to have undergone cytoreductive surgery, and be in clinical complete response or partial response after platinum-based chemotherapy. The patients were randomly assigned 2:1; 206 received olaparib tablets at 300 mg twice daily and 130 received placebo. Olaparib treatment continued until disease progression, and could be stopped in patients showing no evidence of disease at 2 years, although patients with a partial response at 2 years could continue treatment. The primary endpoint was investigator-assessed progression-free survival (PFS) per modified RECIST v1.1. Secondary endpoints were PFS2, which was defined as time from randomisation to second progression event, overall survival, and quality of life.

The primary PFS analysis, done after a median follow-up of 41 months, showed investigator-assessed PFS at 51% data maturity with olaparib was not reached (NR) compared to 13.8 months with placebo (hazard ratio [HR] 0.30; 95% confidence interval [CI], 0.23-0.41; $p < 0.0001$). In addition, median PFS by blinded independent central review (BICR; 38% data maturity) was NR in patients receiving olaparib compared to 14.1 months in patients on placebo (HR 0.28; 95% CI, 0.20–0.39; $p < 0.0001$). Olaparib provided a 70% reduction in the risk of progression or death compared to placebo. PFS2 was also significantly improved with olaparib. Patients demonstrated median PFS2 of NR versus 41.9 months with olaparib versus placebo (HR 0.50; 95% CI, 0.35-0.72; $p = 0.0002$), respectively. Overall survival data were not mature by the time of the congress.

The majority of reported adverse events (AEs) were low-grade; the most common grade ≥3 AEs in the olaparib arm were anaemia, which occurred in 22% of patients and 8% of patients had neutropaenia. Olaparib dose reduction or interruption occurred in 28% and 52% of patients, respectively. Twelve percent of patients discontinued olaparib therapy. NCT01844986. Moore *et al.* Published simultaneously in the *NEJM.*[1] Abstract LBA7_PR

Practice point and future research opportunities

The results of SOLO-1 demonstrate an outstanding improvement in PFS over placebo that was maintained even after the olaparib was stopped at two years. These are outstanding results in a worsening disease setting; not only was olaparib efficacious but it was also

shown to be well tolerated. The findings promise to change practice in this subgroup of patients with newly diagnosed advanced ovarian cancer and a *BRCA* mutation.

Two questions remain: Can this benefit be extended to all high-grade serous carcinomas? From existing results in patients relapsing on PARP inhibitor maintenance in all comers, excellent results for all patients with high grade serous or endometrioid ovarian carcinoma can be anticipated. Also, what is the best maintenance therapy? Standard first-line therapy in many countries is chemotherapy plus bevacizumab maintenance for the majority of women with advanced disease, but the question remains whether maintenance with olaparib alone, or in combination with bevacizumab may be preferable. The PAOLA 1 trial will provide some information, and results will probably be available next year.

Citation:

1. Moore K, Colombo N, Scambia G, *et al.* Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. NEJM 2018; 379:2495-2505.

Lurbinectedin shows similar PFS and ORR as physicians' choice of standard treatment in platinum-resistant ovarian cancer

Lead author Stephanie Gaillard, Gynaecologic Cancer Trials, Duke University Medical Centre, Baltimore, USA presented results of the CORAIL trial of lurbinectedin in women with platinum-resistant ovarian cancer (PROC). Lurbinectedin is an agent of marine origin that blocks transcriptional transactivation, induces DNA double-strand breaks, and modulates the tumour microenvironment that has demonstrated improved anti-tumour activity compared to topotecan in PROC.[1] Patients with PROC with a platinum-free interval (PFI) of 1 to 6 months after the last platinum chemotherapy who had received ≤3 lines of chemotherapy, and ECOG performance status (PS) 0-2 were eligible for CORAIL. Patients were randomly assigned 1:1 with 442 patients per arm. They were treated with lurbinectedin at 3.2 mg/m^2 every 3 weeks or with investigator choice (IC) of either pegylated liposomal doxorubicin (PLD) at 50 mg/m^2 every 4 weeks or topotecan at 1.5 mg/m^2/day on days 1-5 every 3 weeks until progression or treatment discontinuation due to toxicity. Patients were stratified by PS (0 versus ≥1), PFI (1-3 versus >3 to 6 months), and the number of prior chemotherapy lines received (1 or 2 versus 3). The primary endpoint was progression-free survival (PFS) by independent review committee (IRC) and secondary endpoints included objective response rate (ORR), overall survival (OS), and patient-reported outcomes (PROs).

Baseline characteristics were mostly well balanced, with both arms receiving a median of 2 prior chemotherapy lines. There were discrepancies in the lurbinectedin and IC arms regarding median age (63 versus 59 years), serous histology (82% versus 90%), presence of ascites (41% versus 50%), and receipt of prior bevacizumab (40% versus 46%), respectively. The primary endpoint was not met; median PFS was equivalent at 3.5 months with lurbinectedin compared to 3.6 months with IC (hazard ratio [HR] 1.04; 95% confidence

interval [CI], 0.84-1.29). The ORR was 14.0% (95% CI, 9.7-19.3%) versus 12.2% (95% CI, 8.2-17.3%), respectively (p = non-significant). Similar results were seen with lurbinectedin versus IC for the other secondary endpoints: interim OS was 11.2 versus 11.1 months (HR 0.97; 95% CI, 0.77-1.23). Global QoL scores were similar between treatment arms. Lurbinectedin versus IC showed a slightly more tolerable safety profile; the incidence of adverse events (AEs) was 92% versus 93% and the incidence of grade ≥ 3 AEs was 48% versus 64% (p = 0.001). Regarding IC, topotecan accounted for a higher percentage of AEs than PLD. Treatment-related dose reductions, delays, and discontinuations were more frequent with investigators' choice. NCT02421588. Gallard *et al.* Abstract 932O

Practice point and future research opportunities

Although CORAIL did not meet the primary endpoint, similar efficacy results were demonstrated with lurbinectedin and standard IC therapies; taken together with the favourable safety profile these findings suggest there may be a potential role for lurbinectedin in the difficult-to-treat PROC setting. Lurbinectedin is also being investigated in endometrial cancer (*J Clin Oncol*. 35, 2017; suppl abstr 5586), and small-cell lung cancer (ATLANTIS, NCT02566993). Lurbinectedin was granted an orphan drug designation by the FDA for the treatment of patients with small-cell lung cancer in August 2018.

Citation:

1. Poveda A, Del Campo JM, Ray-Coquaed, *et al*. Phase II randomized study of PM01183 versus topotecan in patients with platinum-resistant/refractory advanced ovarian cancer. *Ann Oncol* 2017; 28(6):1280-1287.

Clinical response to pembrolizumab associates with T-cell gene expression profile in patients with advanced recurrent ovarian cancer

Jonathan A. Ledermann, Cancer Trials Centre, Cancer Institute, University College London in London, UK presented interim results from a biomarker analysis of the phase II KEYNOTE-100 trial. Previous findings from this trial showed an association between pembrolizumab response and PD-L1 expression of combined positive score (CPS) ≥10. The analysis presented at ESMO 2018 evaluated the response according to other biomarkers. Patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, and confirmed recurrence following front-line platinum-based therapy were enrolled. Other criteria included ECOG performance status 0/1, and a tumour sample. All patients received intravenous pembrolizumab at 200 mg every 3 weeks for 2 years or until progression, death, unacceptable toxicity, or consent withdrawal. Whole exome sequencing of paired tumour and normal samples determined homologous recombination deficiency genomic scar (HRD) and *BRCA*1/2 mutation status using standard algorithms. Associations of response with a T-cell-inflamed 18-gene expression profile (T-cell-GEP) score, HRD, *BRCA*, and microsatellite instability-high (MSI-H) were evaluated, as well as PD-L1 expression by immunohistochemistry.

This analysis revealed that a CPS ≥10 was associated with response to pembrolizumab. The evaluation included the first 100 enrolled patients with available T-cell-GEP, BRCA, and HRD data, whereas MSI-H data was from all 319 patients in the entire study population. The biomarker analysis showed that responders had a significantly higher distribution of GEP scores than non-responders (1-sided p = 0.03 from Wilcoxon rank sum test). Of these 83 patients, 8.4% of patients demonstrated response. In 79 patients with PD-L1 CPS and GEP (Spearman's correlation ρ=0.57), the area under the receiver characteristic curves for CPS and T-cell-GEP were numerically similar at 0.73 and 0.72, respectively. No statistically significant differences were observed with HRD values among responders and non-responders (1-sided p = 0.29; n=71). No association between *BRCA* status and response was observed (1-sided p = 0.65) in 11 patients with *BRCA* mutation and 60 patients with wild type. In this cohort 6 (8.5%) patients were responders. All 319 paired samples tested for MSI-H were MSS. NCT02674061. Ledermann *et al.* Abstract LBA 36

Practice point and future research opportunities

Findings from this analysis of the first 100 samples and data from KEYNOTE-100 suggest that T-cell-GEP was associated with a response to pembrolizumab monotherapy for treatment of advanced ovarian cancer in a single-arm setting, in addition to PD-L1 CPS. However, HRD biomarkers, including HRD and *BRCA* did not associate with the pembrolizumab response in advanced recurrent ovarian cancer.

Adding bevacizumab to weekly paclitaxel does not significantly improve outcomes in patients with ovarian sex cord tumours

Isabelle L. Ray-Coquard, Medical Oncology, Centre Léon Bérard, Lyon, CEDEX, France, and colleagues conducted the phase II Alienor/ENGOT-ov7 randomised trial of paclitaxel plus bevacizumab compared to paclitaxel monotherapy in patients with ovarian sex cord tumours (SCT). Ovarian SCT have been shown to respond poorly to chemotherapy, prompting this investigation of the efficacy of paclitaxel with and without bevacizumab. This study enrolled 60 patients with SCT; 52 with adult granulosa cell tumour (AGCT), 2 had Sertoli Leydig tumour (SLT), and 6 patients with other tumours. All patients were in relapse following >1 line of platinum-based chemotherapy and were also not candidates for surgery. Seventeen (28%) patients had received prior hormonal therapy and the platinum-free interval (PFI) was ≥ 12 months in 21 (66%) patients. Patients in the paclitaxel arm were allowed to receive bevacizumab alone at progression. The primary endpoint was the progression-free survival (PFS) rate at 6 months (PFR-6).

The PFR-6 was 71% (95% confidence interval [CI], 55–84) with paclitaxel compared to 72% (95% CI, 55–87) with paclitaxel/bevacizumab, and median PFS was 14.7 versus 14.9 months, respectively. In the paclitaxel arm, 50% of patients received bevacizumab monotherapy at cross over; these patients demonstrated median PFS of 7.3 months. The ORR with paclitaxel was 25%, with 53% of patients achieving stable disease (SD) and 22% of patients experiencing progressive disease (PD). With paclitaxel plus bevacizumab, the

ORR was 44%, which included 44% patients with SD and 11% of patients showing PD. The median time to first subsequent therapy was 28.5 months with paclitaxel cross-over to bevacizumab, 33.6 months with paclitaxel monotherapy, and 33.6 months with paclitaxel/bevacizumab.

The most frequent adverse events (AEs) of any grade included hypertension in 78% of patients receiving paclitaxel compared to 93% of patients receiving the combination. In the respective cohorts, the incidence of AEs was fatigue (63% versus 78%), neuropathy (56% versus 74%), proteinuria (13% versus 63%), bleeding (16% versus 59%), alopecia (34% versus 56%), and vomiting (16% versus 7%), respectively. Ten patients on paclitaxel reported grade 3/4 AEs compared to 12 patients receiving paclitaxel/bevacizumab. EudraCT. 2012-002841-39. Ray-Coquard *et al.* Abstract 934O

Practice point and future research opportunities

This study demonstrates the feasibility of conducting a randomised trial in rare cancer and confirmed paclitaxel activity in SCT. The addition of bevacizumab tended to increase response compared to paclitaxel monotherapy but did not significantly improve PFR-6 or PFS in relapsed SCT patients.

Immunotherapy may represent a paradigm change in treatment of patients with chemotherapy resistant gestational trophoblastic neoplasia

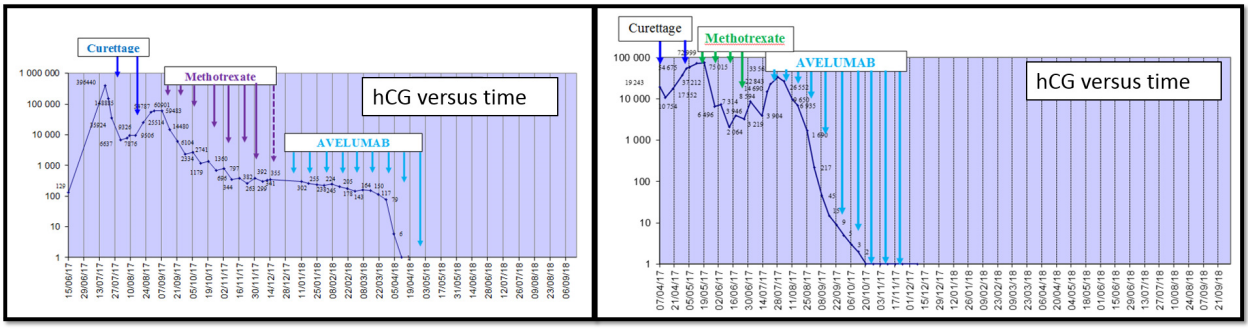
Benoit You, Hospices Civils de Lyon in Lyon, France and colleagues from the French Gestational Trophoblastic Disease (GTD) Centre led by Francois Golfier are conducting the academic phase II, multicentre TROPHIMMUN trial to evaluate the efficacy of avelumab in patients with chemoresistant gestational trophoblastic neoplasia (GTN). The rationale for this study is that PD-L1 is constitutively expressed in all GTN subtypes.[1] Gestational trophoblastic diseases (GTD) represent a group of rare tumours that accounts for less than 1% of female reproductive system cancers. GTD involves abnormal growth of cells arising within the uterus following conception. GTD tumours grow in the cells that would normally develop into the placenta during pregnancy, rather than from cells of the uterus or cervix.

As of September 2018, cohort A of TROPHIMMUN had enrolled 11 patients with GTN who had demonstrated resistance to monochemotherapy, and cohort B had enrolled 4 patients with polychemotherapy resistant GTN. All patients in cohort A had post-molar diagnosis of GTN based on increased human chorionic gonadotropin (hCG), 63% of patients had stage I, 27% had stage III, and 9% had stage IV disease; 45% of patients had FIGO score 1-4, and 55% had FIGO score 5-6 disease. All patients had shown prior resistances to methotrexate and 9% of patients had been resistant to actinomycin-D treatment. The median age of the patients was 33 (range, 27 to 55) years. All patients were treated with avelumab at 10 mg/kg every 2 weeks until normalisation of hCG levels was achieved, and for 3 additional cycles thereafter. Since achieving hCG normalisation is associated with a

high chance of disease cure, the rate of hCG normalisation served as the primary endpoint of the ongoing 2 step Simon design study.

At ESMO 2018 Congress, Professor You presented the results of a pre-planned intermediate analysis of data from the first 6 patients treated with avelumab in cohort A (Figure). Among these patients, 3 patients attained normalised hCG and stopped treatment with no further indication of relapse within a 11.7 month follow-up. The other hCG declines observed in subsequently recruited patients remain to be confirmed.

Figure : hCG values versus time curves of 2 illustrative patients successfully treated with avelumab in cohort A



© Benoit You

The investigators noted that TROPHIMMUN is the first clinical trial to report potential cures with a non-chemotherapy agent in patients with this rare cancer. GTN patients that are resistant to chemotherapy generally receive standard treatment with historic single agent or polychemotherapy regimens, which are known to be effective in achieving 65% to 95% successful hCG normalisation. However, these regimens are also associated with high toxicity.

The adverse events profile observed in all enrolled patients in cohort A was in line with the favourable toxicity profile reported with avelumab to date. Eight (73%) patients experienced 63 adverse events (AEs); 84% were grade 1 AEs, and 14.0% were grade 2 AEs, including one case of hypothyroidism, and one grade 3, disease-related metrorragia.

Since PD-L1 is expressed in GTN, there is a strong rational for investigating immunotherapies in GTN patients. The on-going translational research projects led by Pierre-Adrien Bolze, from the French GTD centre, should help better select the patients who will benefit the most from avelumab. NCT03135769; EudraCT Number, 2016-002322-37. You *et al.* Abstract LBA35

Practice point and future research opportunities

The preliminary results from cohort A of the TROPHIMMUN trial suggest that avelumab may be effective and better tolerated than standard chemotherapy in patients with resistance to single chemotherapy. This study involves rare cancers in young patients who may possibly have immune tolerance derived from pregnancy. There is a lack of level 1 evidence in rare tumours and confounding factors for treatment-related outcomes. The authors are to be congratulated for performing this study in rare tumours and expanding the study to a global level may achieve stronger evidence.

Citation:

1. Bolze PA, Patrier S, Massardier J, *et al.* PD-L1 Expression in Premalignant and Malignant Trophoblasts From Gestational Trophoblastic Diseases Is Ubiquitous and Independent of Clinical Outcomes. *Int J Gynecol Cancer* 2017; 27(3): 554-561.

HAEMATOLOGICAL MALIGNANCIES

Frontline VR-CAP outperforms R-CHOP in transplantation-ineligible patients with newly diagnosed mantle-cell lymphoma

Lead author Franco Cavalli, Oncology, IOSI - Ospedale Regionale Bellinzona e Valli, Bellinzona, Switzerland presented the final overall survival (OS) and safety results from the LYM-3002 study. The randomised, open label phase III study compared the efficacy and safety of first-line bortezomib plus rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP**)** versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in transplant-ineligible patients with untreated mantle-cell lymphoma (MCL). These findings represent a long-term follow-up phase after the primary progression-free survival (PFS) endpoint was achieved.

From May 2008 to July 2017, the trial enrolled adult treatment-naïve patients with a confirmed stage II–IV MCL diagnosis, and an ECOG performance status of ≤2, who were ineligible for bone marrow transplantation. A total of 487 patients were randomised; 244 patients were treated with 6 or 8 (21-day) cycles of VR-CAP comprising rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2, doxorubicin at 50 mg/m^2, prednisone at 100 mg/m^2 plus bortezomib at 1.3 mg/m^2 and 234 patients received the R-CHOP regimen of rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2, doxorubicin at 50 mg/m^2, prednisone at 100 mg/m^2 and vincristine at 1.4 mg/m^2 to a maximum of 2 mg.

The follow-up analysis included 140 and 128 patients treated with VR-CAP and R-CHOP, respectively. With a median follow-up of 82 months, 241 OS events had occurred, 42% of events with VR-CAP and 57% with R-CHOP. The median OS improved significantly with VR-CAP to approximately 3 years longer than with R-CHOP; median OS was 90.7 months with VR-CAP versus 55.7 months with R-CHOP (hazard ratio [HR] 0.66; 95% confidence interval [CI], 0.5-0.85; p = 0.001). Subsequent treatments were required for 104 (43%) patients receiving VR-CAP compared to 151 (62%) patients on R-CHOP.

Overall, 20 patients had second primary malignancies. In the VR-CAP cohort, one lung adenocarcinoma and one gastric cancer occurred, both grade 4. One grade 2 pneumonia was reported with R-CHOP. Three patients treated with VR-CAP and 5 patients receiving R-CHOP died on study. NCT00722137. Cavalli *et al.* Published simultaneously in the *Lancet Oncology.*[1] Abstract 1004O

Practice point and future research opportunities

VR-CAP demonstrated a statistically significant and robust survival benefit over R-CHOP for transplant-ineligible patients with untreated MCL, along with an expected and manageable safety profile. These long-term findings taken together with the previously reported PFS results, establish VR-CAP as a preferred treatment option in this patient population.

Citation:

1. Robak T, Jin J, Pylypenko H, *et al.* Frontline bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in transplantation-ineligible patients with newly diagnosed mantle cell lymphoma: final overall survival results of a randomised, open-label, phase 3 study. *Lancet Oncology* 2018; 19(11):1449-1458.

Copanlisib monotherapy shows promising activity in relapsed and/or refractory indolent B-cell lymphoma

Pier Luigi Zinzani, Institute of Hematology 'L.e A. Seragnoli', University of Bologna, Bologna, Italy explained that copanlisib monotherapy has been investigated in four phase I or II studies in patients with relapsed or refractory (r/r) indolent B-cell lymphoma who progressed on 2 or more prior lines of therapy. Comparison of data from these trials was possible in this safety and efficacy analysis due to all 4 trials having similar entry criteria. Patients with indolent B-cell non-Hodgkin lymphoma that was r/r to ≥2 prior lines of treatment, including rituximab and an alkylating agent, were eligible. Copanlisib was administered intravenously intermittently on days 1, 8, and 15 of a 28-day cycle at either 0.8 mg/kg in three studies or as a flat 60 mg dose in one study. The primary efficacy endpoint was objective response rate (ORR) using Cheson criteria based on central independent review and/or investigator assessment. The full analysis set comprised 126 patients with follicular and 26 patients with marginal zone lymphoma. The patients' median age was 64 (range, 25 to 82) years, and the ECOG performance status was 0 or 1 in 56% and 40% of patients, respectively.

The efficacy analysis demonstrated an objective response rate (ORR) by central independent review of 60% for the entire patient population. Twenty-one (12%) patients achieved complete response (CR) and one patients had an unconfirmed CR, 79 (47%) patients showed partial response (PR), and 51 (30%) patients had stable disease (SD). The ORR according to investigator assessments was 54%, with 9 (5%) CR, 81 (48%) PR, and 54 (32%) SD.

The most commonly occurring grade 3/4 treatment emergent adverse events (TEAEs) included transient hyperglycaemia in 32% and 6% of patients, as well as transient hypertension in 27% and 0 patients, respectively. Other AEs (all grade/grade 3/grade 4) occurring in >25% of patients included diarrhoea (36/5/0), fatigue (29/3/0), and nausea (26/1/0). Serious AEs of interest included pneumonia (10/7/1), pneumonitis (6/3/0), respectively, and one grade 4 case of colitis. NCT00962611, NCT02155582, NCT01660451. Zinzani *et al.* Abstract 1006O

Practice point and future research opportunities

Treatment of indolent B-cell lymphoma patients with copanlisib administered intermittently and intravenously resulted in a manageable and predictable safety profile, with a low incidence of severe gastrointestinal-related toxicities. The response to copanlisib was robust

by both independent and investigator analysis in patients with indolent lymphoma. Further investigation in larger, randomised, controlled trials is warranted.

HEAD AND NECK CANCER

First-line pembrolizumab as monotherapy or combined with chemotherapy improves OS compared to current standard of care in recurrent/metastatic HNSCC

Barbara Burtness, Yale School of Medicine, Development Therapeutics Research Program, Yale Cancer Centre in New Haven, US and an international research team conducted the phase III KEYNOTE-048 study examining whether the anti-PD-1 monoclonal antibody pembrolizumab administered as monotherapy or in combination with chemotherapy may improve benefit over the current standard of care as front-line treatment of patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). The trial enrolled patients with R/M HNSCC who were not curable by local therapy and had not received prior chemotherapy or biologic therapy for recurrent or metastatic disease. Patients were randomised equally to receive one of 3 treatments: 301 patients were treated with pembrolizumab at 200 mg every 3 weeks, 281 patients received the pembrolizumab regimen plus chemotherapy comprising 5-fluorouracil (5-FU) at 1000 mg/m^2/day for 4 days every 3 weeks together with 100 mg/m^2 cisplatin or carboplatin AUC 5 every 3 weeks, and 300 patients received cetuximab at 400 mg/m^2 loading followed by 250 mg/m^2 weekly plus chemotherapy (EXTREME, current standard). The primary end points for pembrolizumab versus EXTREME and pembrolizumab/chemotherapy versus EXTREME were progression-free survival (PFS) and overall survival (OS) in patients with PD-L1 combined positive score (CPS) ≥20, CPS ≥1, and the total population.

The minimum follow-up for this final PFS/interim OS analysis was approximately 17.0 months. For the comparison of pembrolizumab versus EXTREME in the subgroup of 255 patients with a CPS >20 of PD-L1 expression on tumour and/or surrounding cells, pembrolizumab significantly improved OS; median OS was 14.9 months with pembrolizumab compared to 10.7 months with EXTREME (hazard ratio [HR] 0.61; 95% confidence interval [CI], 0.45-0.83; p = 0.0007). However, since pembrolizumab did not prolong PFS over EXTREME (p = 0.5) no further PFS testing was done for pembrolizumab versus EXTREME per the analysis plan. Although the ORR was lower with pembrolizumab versus EXTREME (23.3% versus 36.1%), the median duration of response (DoR) was considerably longer with pembrolizumab at 20.9 months, compared to 4.5 months with EXTREME.

Similar results were observed in 512 patients with a lower cut point (CPS > 1). Median OS was 12.3 and 10.3 months with pembrolizumab and EXTREME (HR 0.78; 95% CI, 0.64-0.96; p = 0.0086). The confirmed ORR was 19.0 with pembrolizumab compared to 36 months with EXTREME and the DoR was 20.9 versus 4.5 months, respectively. Analysis of pembrolizumab versus EXTREME in the 601 patients in the overall population irrespective of PD-L1 expression demonstrated that OS with pembrolizumab was non-inferior to EXTREME; the ORR was 17% versus 36%, and DoR was 20.9 versus 4.5 months, respectively.

The comparison of the pembrolizumab plus chemotherapy versus EXTREME in patients with PD-L1 CPS ≥20 and CPS ≥1, showed that OS was not statistically superior with the pembrolizuab combination, nor was PFS significantly longer (p = 0.2). Comparison of data from 281 patients receiving pembrolizumab plus chemotherapy and 278 receiving EXTREME in the overall population showed median OS of 13.0 months versus 10.7 months (HR 0.77; 95% CI, 0.63-0.93; p = 0.0034). The ORRs were 35.6% and 36.3% with pembrolizumab/chemotherapy versus EXTREME, and the DoR was 6.7 months versus 4.3 months, respectively. Pembrolizumab plus chemotherapy versus EXTREME demonstrated that OS with the pembrolizumab combination was non-inferior to EXTREME in the total population.

Pembrolizumab was well tolerated with a safety profile that was consistent with prior studies. The combination of pembrolizumab and chemotherapy had a comparable safety profile to EXTREME. The rates of grades 3 to 5 treatment-related adverse events (TRAEs) were 71% with pembrolizumab monotherapy, 69% for patients who received EXTREME, and 71% in the pembrolizumab/chemotherapy group. NCT02358031. Burtness *et al.* Abstract LBA8_PR

Practice point and future research opportunities

This is the first study to show superior OS over the decade-old standard of care, platinum-based chemotherapy and cetuximab, and establishes PD-L1 CPS as a valid marker for head and neck cancer that should be routinely measured in these patients.The challenge is that treatment benefit is not equally distributed but depends on a biomarker. Hence, PD-L1 CPS expression will likely inform the choice between the two new options – pembrolizumab alone, with a favourable side effect profile, and pembrolizumab combined with chemotherapy, which may be used in a larger group of patients. Higher PD-L1 expression is associated with more benefit but the exact cut points have to be determined, and individual patient characteristics will play an important role as well. Separate analyses are needed in patients who have tumours with low or absent PD-L1 expression, where there is potentially less benefit. The usefulness of other biomarkers to select patients for treatment, such as tumour mutational burden, should also be examined.

Cetuximab should not replace cisplatin as standard of care in patients with HPV-positive, low risk oropharyngeal cancer, receiving radical radiotherapy

Hisham Mehanna, Institute of Cancer and Genomic Sciences, The University of Birmingham, Birmingham, UK noted that the incidence of Human papillomavirus-positive oropharyngeal cancer (HPV-positive OPSCC) is rapidly rising. HPV-positive OPSCC represents a distinct disease entity, affecting younger patients who achieve better outcomes. However, the standard treatment of cisplatin plus radiotherapy causes significant toxicity, with effects that remain with these young patients for decades. The epidermal growth factor receptor inhibitor, cetuximab has been proposed for treatment de-escalation to reduce toxicity of standard treatment, prompting Dr. Mehanna and colleagues to conduct this international, multicentre, randomised, controlled trial. The trial randomised 334 patients with low-risk HPV-positive OPSCC to receive radiotherapy at 70 Gy in 35 fractions plus either cisplatin at 3 doses of 100 mg/m^2 (n=166), or cetuximab at a 400 mg/m^2 loading dose followed by weekly 250 mg/m^2 doses (n=168). The patient demographics were well balanced between arms; 80% of patients were male, with a mean age of 57 years. Outcomes included the total number of severe grades 3-5 toxicity events, overall survival (OS), and quality of life (QoL).

In the cisplatin arm, 10 disease recurrences and 6 deaths occurred compared to 29 recurrences and 20 deaths with cetuximab. The 2-year OS differed significantly, favouring cisplatin; 2-year OS was 97.5% with cisplatin versus 89.4% with cetuximab (HR 4.99; 95% CI, 1.70-14.67; p = 0.001), as did the 2-year recurrence rate of 6.0% versus 16.1%, respectively (HR 3.39; 95% CI, 1.61-7.19; p = 0.0007).

The reported mean number of overall events per patient was 5.37 versus 5.45 and the mean number of acute or late severe (grades 3 to 5) toxicity events per patient or all grade toxicity was 29.15 versus 30.05 events per patient, respectively, with cisplatin and cetuximab. Significantly more (162) serious adverse events occurred with cisplatin compared to 95 with cetuximab. ISRCTN33522080. Mehanna *et al.* Abstract LBA9_PR.

Practice point and future research opportunities

It was believed that cetuximab caused fewer side effects and was a good option for HPV-positive throat cancer for patients who are young and expected to survive for several decades, as well as those less able to tolerate chemotherapy. However; this study shows that the best treatment choice for patients with HPV-positive throat cancer is cisplatin and radiotherapy. This combination is more effective in terms of survival and did not worsen all grade toxicity compared to cetuximab with radiotherapy. These results are in agreement with interim findings of the US National Cancer Institute's RTOG 1016 trial.[1] There are now two studies showing that these patients should not be given cetuximab. Future research should examine whether genotyping for the KRAS-variant can select a group of patients that will benefit from cetuximab treatment with radiotherapy. Cisplatin and radiotherapy remain the standard of care in patients with HPV-positive OPSCC.

Citation:

1. Presented during the plenary session at the American Society for Radiation Oncology (ASTRO) annual meeting on 22 October 2018.

Preoperative olaparib as monotherapy or in combination with cisplatin shows promising anti-tumour activity in patients with operable HNSCC

Amanda Psyrri, Internal Medicine/Medical Oncology, Attikon University Hospital, Athens, Greece presented findings from the phase II window of opportunity OPHELIA study of preoperative olaparib plus either cisplatin or durvalumab and olaparib as monotherapy in patients with operable squamous cell head and neck carcinoma (HNSCC). OPHELIA randomised 23 patients 3:3:3:1 to one of 4 treatment regimens: cisplatin at 60 mg/m^2 on day 1 followed by olaparib at 75 mg on days 1-5, olaparib at 300 mg twice daily for 21-28 days, durvalumab at 1500 mg on day 1 followed by olaparib at 600 mg daily for 21-28 days, or no treatment. Peripheral blood mononuclear cells (PBMCs) were isolated from blood obtained from patients at diagnosis, at week 24, and at 3 weeks following treatment. Double Stranded Brakes/Repair (DSB/R) was measured using phosphorylation of histone H2AX by immunofluorescence and confocal laser microscope analysis, and/or comet assay while Nucleotide Excision Repair (NER) efficiency was measured by southern blotting.

This ongoing study is continuing recruitment. The 23 enrolled patients have a median age of 61.2 years, 87% use tobacco, 4, 4, 2, 11, and 2 patients were cT1, cT2 , cT3, cT4, and cTx, respectively. Fifteen patients are cN0/1 and 8 are cN2. Thus far, 12 patients have been randomised to olaparib monotherapy, 8 patients to cisplatin plus olaparib, and 3 patients to no treatment. Preliminary findings to date indicate no serious study drug-related adverse events or unexpected surgical delays/complications have occurred. Data from the durvalumab arm are not yet mature. The efficacy analysis revealed that downstaging was possible in 4 (17%) patients; of these, 3 are receiving olaparib and one patient is on cisplatin plus olaparib. One patient receiving olaparib has achieved pathological complete response, one patient demonstrated partial response, 15 patients had stable disease post treatment, and 2 patients had progressive disease. Results are not yet available for 2 patients.

Evaluation of the PBMCs revealed significantly increased ongoing spontaneous DNA damage in the PBMCs from untreated patients compared to healthy controls. Differences in cisplatin-induced DNA damage levels were found among patients. Similar formation of monoadducts was found at 3-hours in ex-vivo cisplatin treatment of PBMCs from untreated patients; thereafter, their levels were decreased, with removal capacity being higher in healthy controls than in patients. NCT02882308. Psyrri *et al.* Abstract 1045O

Practice point and future research opportunities

Neoadjuvant olaparib with or without cisplatin has been well tolerated to date and has provided promising anti-tumour responses. Higher levels of spontaneous ongoing DNA damage was noted in HNSCC patients compared to controls, which may, with further study, serve as a candidate biomarker for response to immunotherapy in HNSCC.

Tipifarnib shows promising anti-tumour activity in HNSCC harbouring *HRAS* mutations

First author Alan L. Ho, Memorial Sloan Kettering Cancer Centre, New York, USA, explained that novel tipifarnib is a first-in-class potent and highly selective inhibitor of farnesyltransferase inhibitor (FTI), which is an enzyme critical for the proper function of *HRAS*, a proto-oncogene that is overexpressed and mutated in head and neck squamous cell carcinomas (HNSCC) and other cancers. Although *HRAS* was discovered over 40 years ago, no therapies are yet approved that directly target mutant *HRAS.* This phase II trial evaluated tipifarnib activity in patients with *HRAS*-mutant tumours across 2 cohorts: cohort 1 included patients with thyroid cancer and cohort 2 had patients with other solid tumours.

Eligible patients had *HRAS* mutation, locally advanced/unresectable and/or metastatic disease, and RECIST v1.1 measurable disease. Tipifarnib was given orally to all patients at 900 mg twice daily on days 1 to 7 and 15 to 21 of a 28-day cycle. The primary endpoint for the study was objective response rate (ORR). The study had a 2-stage design and was considered to be positive when 4 responses were observed in any cohort. In all, 37 patients were treated as of 1 May 2018, including 11 with *HRAS* mutated HNSCC and 2 patients with *HRAS* mutated squamous cell carcinomas (SCC). Of these, 7 HNSCC patients were evaluable for efficacy.

Five (71%) patients achieved a confirmed partial response. In these responding patients, the median duration of response was 14.1 months (95% confidence interval [CI], 1.4-17.3), which exceeded the pre-specified null hypothesis. Importantly, no patient with *HRAS* mutated HNSCC had demonstrated an objective response with their last therapy prior to receiving tipifarnib; the prior regimens included platinum, immunotherapy, and cetuximab with and without chemotherapy.

Tipifarnib was generally well tolerated, with fatigue, myelosuppression, nausea, and vomiting constituting the most common all grade adverse events. The study met its predefined criteria for success and has been amended to continue enrolling patients with *HRAS* mutant HNSCC, as well as patients with SCC other than HNSCC plus *HRAS* mutations into a new cohort 3. NCT02383927. Ho *et al.* Abstract 1046O

Practice point and future research opportunities

Tipifarnib demonstrated encouraging anti-tumour activity among patients with *HRAS*-mutant HNSCC in this ongoing phase II trial. This is the first evidence to really demonstrate that mutant *HRAS* is a target in cancer with FTIs.

IMMUNOTHERAPY OF CANCER

Neoadjuvant ipilimumab plus nivolumab has robust anti-tumour activity in early stage mismatch repair deficient colon cancer

Myriam Chalabi, the Netherlands Cancer Institute, Amsterdam, Netherlands and colleagues conducted the first neoadjuvant study to test ipilimumab plus nivolumab in early stage mismatch repair deficient (dMMR) and MMR proficient (pMMR) colon cancers. The trial treated 14 patients with resectable early-stage colon cancer with nivolumab at 3 mg/kg twice daily on days 1 and 15 and ipilimumab at 1 mg/kg on day 1 prior to surgery, which had been planned at a maximum of 6 weeks after informed consent. The primary endpoints were safety and feasibility, while efficacy as assessed by pathological response criteria, associations between response and tumour mutational burden (TMB), interferon gama (IFN_γ) gene signatures, T-cell infiltration, and T-cell receptor (TCR) clonality served as secondary endpoints.

Of the 8 patients with pMMR and 7 patients with dMMR tumours, 14 patients have been treated with the immunotherapy combination. Major pathological responses, which were defined as <5% of viable tumour cells remaining, have been achieved by 100% of the patients with dMMR colon cancer. Four of these dMMR tumours were clinically stage IIIB/C before treatment initiation. Four (57%) of these patients demonstrated complete responses. No major pathological responses were seen in patients with pMMR tumours. However, both pMMR and dMMR tumours displayed significant increases in T-cell infiltration, particularly CD8+ T-cells; the median fold change was 2.4 ($p = 0.018$) and 4.8 ($p = 0.0009$), respectively. Despite the major difference in TMB between dMMR and pMMR tumours ($p = 0.008$), pre-treatment TCR clonality and IFN_γ gene signatures did not differ substantially between these tumours. In contrast, post-treatment IFN_γ signatures increased the ability to distinguish responders with dMMR from non-responders (pMMR). All of the patients treated with the combination proceeded without delay to radical resection of their tumours. The immunotherapy treatment was well-tolerated.

Short-term, neoadjuvant ipilimumab plus nivolumab resulted in major pathological responses in 100% of dMMR tumours and did not compromise surgery. These findings suggest that neoadjuvant immunotherapy in dMMR colon cancer warrants further research and has the potential to change the current standard of care. The finding that dMMR status and TMB were associated with response, suggest that pre-treatment measures of tumour inflammation may have limited predictive value. NCT03026140. Chalabi *et al.* Abstract LBA37_PR

Practice point and future research opportunities

The study positions immunotherapy at an earlier stage of the disease history for patient with localised disease, and, interestingly, in the neoadjuvant setting as opposed to the adjuvant setting that is now approved in melanoma and non-small cell lung cancer. For dMMR

deficient tumours, the results were amazing, with 100% of patients so far having either complete or near complete responses within the short time frame of treatment, which is usually 4 weeks. These findings may have implications for clinical practice in the future. However, this study is limited by the small size and by being neither randomised nor controlled. Limited data are available but if they show complete pathological responses in the neoadjuvant setting, this therapeutic strategy might become standard of care for dMMR colorectal cancer. dMMR tumours are more frequent in localised cancers, occurring in approximately 15% of patients than at the metastatic stage, where they are seen in about 5% of patients.

Trastuzumab plus nelipeptimut-S (NeuVax) improves DFS over trastuzumab in triple negative, HER2 low-expressing breast cancer patients

Lead author Dianne F. Hale, General Surgery, San Antonio Military Medical Centre, San Antonio, USA explained that HER2 low-expressing (immunohistochemistry 1-2+, non-amplified) breast cancer patients are not eligible for HER2-targeted therapies. Her research team has shown that the HER2-derived nelipeptimut-S (E75) plus GM-CSF (NeuVax) is safe, immunogenic, and displayd synergistic activity with trastuzumab in pre-clinical and pilot clinical studies. At ESMO 2018, Dr. Hale reported the results of an interim analysis of a multicentre, prospective, randomised, single-blinded, placebo-controlled phase IIb trial comparing trastuzumab plus NeuVax to trastuzumab monotherapy in patients with HER2 low-expressing, node positive (NP) and/or triple negative breast cancer (TNBC). The trial enrolled 275 patients who were randomised equally to receive trastuzumab plus NeuVax (vaccine arm; n=136) or trastuzumab plus GM-CSF (control arm, n=139). All patients received 1 year of trastuzumab per label and NeuVax or GM-CSF was given every 3 weeks for 6 cycles starting with 3rd trastuzumab dose, then boosted every 6 months for 4 cycles. Cardiac ejection fraction (EF) was measured at baseline and serially on study. This re-specified interim analysis was done 6 months after the last enrolment on data from the intent-to-treat (ITT) and modified ITT/safety (mITT/S); which included patients receiving ≥1 dose of NeuVax or GM-CSF. The primary endpoint was disease-free survival (DFS) at 24 months.

At a median follow-up of 19.4 months the estimated 24 month DFS was 88.6% with the vaccine combination compared to 82.5% with trastuzumab/GM-CSF in the ITT population (hazard ratio [HR] 0.67; p = 0.26) and 89.3% versus 82.3%, respectively in the mITT/S population (HR 0.61; p = 0.17). In node-positive patients, the estimated 24 month DFS was 85.9% versus 80.2% (HR 0.71; p = 0.38), in the vaccine versus control arms, respectively. However, TNBC patients did show a response to the vaccine by demonstrating a 24 month DFS rate of 91.1% with trastuzumab plus NeuVax versus 69.9% with trastuzumab/GM-CSF (HR 0.26; p = 0.02). No difference between groups was observed in treatment related local (p = 0.19) or systemic (p = 0.85) toxicities, or in pre- to post-treatment ejection fraction (p = 0.60); no grade 4/5 events occurred. NCT01570036. Hale *et al.* Abstract 1128O

Practice point and future research opportunities

The NeuVax vaccine administered with trastuzumab is safe and does not display additional cardiac toxicity compared to trastuzumab in the long term. This analysis shows interesting but not statistically significant efficacy trends that favour the combination. The significant clinical benefit in patients with TNBC warrants definitive further investigation in a large phase III study.

MELANOMA

Optimal neo-adjuvant combination of ipilimumab and nivolumab devised in high-risk melanoma

Christian Blank, Medical Oncologist, The Netherlands Cancer Institute in Amsterdam, Netherlands, an author on the study, pointed out that patients with high-risk stage III melanoma generally have poor outcomes with a 5-year overall survival rate of less than 50%. The multicentre phase II, OpACIN-neo trial assessed three dosing regimens of nivolumab and ipilimumab to reduce toxicity while retaining the high response rates demonstrated in stage III melanoma. In the previous phase Ib OpACIN study, neoadjuvant ipilimumab plus nivolumab treatment provided a pathological response rate (pRR) of 78%, and none of the patients in the trial demonstrating pathologic response have relapsed to date.[1] However, toxicity was high, with 90% of patients experiencing grade 3/4 immune-related adverse events (irAEs), leading the investigators to evaluate alternative dosing regimens in the OpACIN–neo trial.

In OpACIN-neo, patients with resectable macroscopic stage III melanoma were randomly assigned 1:1:1 to receive standard therapy comprising 2 doses of ipilimumab at 3 mg/kg plus nivolumab at 1 mg/kg every 3 weeks (arm A), or 2 doses of ipilimumab at 1 mg/kg plus nivolumab at 3 mg/kg every 3 weeks (arm B), or to receive 2 doses of ipilimumab at 3 mg/kg every 3 weeks followed immediately by 2 doses of nivolumab at 3 mg/kg every 2 weeks (arm C). Eligible patients were required to have one or more measurable lymph node metastases (RECIST v1.1), no in-transit metastases within the last 6 months, and normal LDH. Complete lymph node dissection was scheduled at week 6. The primary endpoints were grade ≥3 irAEs within the first 12 weeks, radiologic RR according to RECIST v1.1, and pRR, which was defined as less than 50% of viable tumour cells remaining.

This analysis included data from 86 patients with evaluable data: 30 patients in each of arms A and B, and 26 in arm C. At a median follow-up of 7.7 months, the Data Safety Monitoring Board recommended early closure of arm C due to toxicity. Grade ≥3 irAEs had occurred in 40%, 20%, and 50% of patients in arms A, B, and C, respectively. The radiologic and pathologic response was also lowest in arm C; the radiologic RR was 60%, 60%, and 42%, and the pRR was 80%, 77%, and 68% in arms A, B, and C, respectively. Pathological complete response (pCR) was achieved by 47% of patients in arm A, 57% in arm B, and by 23% of patients in arm C. None of the patients achieving pRR have relapsed; however, relapse has been reported in 9 of 21 patients demonstrating no pRR.

Two deaths occurred in arm A; one patient who did not have a pRR died of melanoma and one pCR patient died due to complications after experiencing immune-related encephalitis at 9.5 months following the initiation of therapy. Data from the OpACIN-neo study led the investigators to conclude that the arm B combination of neoadjuvant ipilimumab at 1 mg/kg plus nivolumab at 3 mg/kg resulted in less toxicity than the standard dosing regimen.

Furthermore, the high RR was preserved with this regimen. NCT02977052. Rozeman *et al.* Abstract LBA42

Practice point and future research opportunities

Findings from this study suggest that neoadjuvant ipilimumab at 1 mg/kg plus nivolumab at 3 mg/kg maintained the RR while providing less toxicity than the standard dosing regimen in stage III melanoma. This schedule warrants further testing against adjuvant PD-1 blockade agents in a phase III study.

Regarding pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma, it remains questionable whether pCR as is used in neoadjuvant chemotherapies, accurately predicts long term survival, which is not the case in neoadjuvant treatments for breast or pancreatic cancers. Earlier trials of neoadjuvant ipilimumab plus nivolumab identified the regimen with the optimal benefit/risk ratio. However, long-term benefit value of pCR remains to be proven. This study represents a period of intense "paradigm shaking", and the role of surgery should be revisited.

Citation:

1. Rozeman, Fanch, van Akkoo, *et al*. (Neo-)adjuvant ipilimumab + nivolumab (IPI+NIVO) in palpable stage 3 melanoma – updated relapse free survival (RFS) data from the OpACIN trial and first biomarker analyses. *Annals of Oncology*, 2017; 28(suppl_5):v428-448.

Long-term update from the COMBI-AD trial shows continued RFS with adjuvant dabrafenib plus trametinib in resected BRAF V600 mutated stage III melanoma

Georgina V. Long, Department of Medical Oncology, Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, North Sydney, NSW, Australia, presented an analysis of relapse-free survival (RFS) with extended follow-up, a cure-rate model, and a biomarker analysis from the COMBI-AD trial. The rationale for the COMBI-AD came from two randomised, phase III trials which showed that treatment with dabrafenib plus trametinib improved overall survival in patients with unresectable or metastatic melanoma associated with *BRAF* V600E or V600K mutations; however, whether the therapy improved survival in stage III (resectable) melanoma remained unresolved. The international COMBI-AD trial randomised 870 patients with resected, *BRAF*-mutant melanoma to dabrafenib plus trametinib (n=438) or placebo (n= 432). The previously reported primary analysis demonstrated a 3-year RFS rate of 58% with the combination compared to 39% with placebo (hazard ratio [HR] 0.47, 95% confidence interval [CI], 0.39-0.58; $p < 0.001$).[1] Based on these results, the FDA approved the combination of dabrafenib and trametinib in April 2018 for the adjuvant treatment of patients with *BRAF* V600E– or V600K–mutated stage III melanoma following complete resection.

Subsequently, updated and new analyses were done to characterise the longer-term outcomes. These analyses were done at a median follow-up of 44 months and 42 months for the combination versus placebo arms, respectively. It showed that median RFS was not reached (NR; 95% CI, 46.9 months-NR) in patients receiving dabrafenib plus trametinib compared to 16.6 (95% CI, 12.7-22.1) months with placebo (HR 0.49; 95% CI, 0.40-0.59). The updated analysis showed relapse/death rates of 41% and 59% for the combination and placebo arms, respectively. A Weibull mixture cure-rate model was used to estimate the proportion of patients who will not relapse, which produced cure rate estimates of 54%(95% CI, 49%-59%) for dabrafenib/trametinib and 37% (95% CI, 32%-42%) for placebo.

The mutational landscape and gene expression signatures (GES) were examined in baseline tissue samples by sequencing 570 genes and gene expression profiling (GEP) with a NanoString® panel. DNA sequencing, GEP, and paired DNA plus RNA results were available for 368, 507, and 301 patients, respectively. The biomarker analysis showed that MAP kinase gene alterations were not associated with outcome in the adjuvant setting but did suggest that a high tumour mutational burden (TMB) in association with high levels of interferon-gamma (IFN-γ) might be predictive of greater benefit. In the placebo arm, high IFN-γ and high TMB associated with longer RFS, whereas IFN-γ gene signature identified patients with longer RFS independently of TMB status in the dabrafenib/trametinib arm. An exploratory analysis of RFS in both arms in all TMB/IFN-γ subgroups suggested that low TMB or high TMB/high IFN-γ may be associated with greater RFS benefit than high TMB/low IFN-γ. NCT01682083. Long *et al.* Published simultaneously in the *Journal of Clinical Oncology.*[1] Abstract LBA43

Practice point and future research opportunities

Longer-term follow-up in the COMBI-AD trial confirmed the RFS benefit with adjuvant dabrafenib and trametinib in patients with resected stage III *BRAF*-mutated melanoma. *MAPK* gene alterations previously associated with targeted therapy resistance were not associated with outcome in the adjuvant setting. TMB and immune GES identified patients at higher risk of relapse only in the placebo arm. As yet, there is no biomarker to inform treatment selection; therefore, further investigation is warranted.

Citation:

1. Hauschild A, Dummer R, Schadendorf D, *et al.* Longer Follow-Up Confirms Relapse-Free Survival Benefit With Adjuvant Dabrafenib Plus Trametinib in Patients With Resected *BRAF* V600–Mutant Stage III Melanoma. *JCO* 2018; 36(35):3441-3449.

CheckMate 067 demonstrates continued survival benefit with nivolumab plus ipilimumab and sole nivolumab over ipilimumab monotherapy in advanced melanoma

Results after a minimum follow-up of 48 months presented by Frank Stephen Hodi, Department of Medical Oncology, Dana-Farber Cancer Institute in Boston, USA showed

that nivolumab administered in combination with ipilimumab or alone continued to show improved survival benefit over ipilimumab monotherapy.

CheckMate 067 randomised 945 patients with unresectable stage III or stage IV melanoma. Randomisation was stratified by PD-L1 status, *BRAF* mutation status, and melanoma stage. A total of 314 patients were treated with nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab at 1 mg/kg every 3 weeks, 316 patients received nivolumab at 3 mg/kg every 2 weeks plus placebo, and 315 patients received ipilimumab at 3 mg/kg plus placebo every 3 weeks for 4 doses.

The co-primary endpoints, overall survival (OS) and progression-free survival (PFS) were met, as previously reported; OS, PFS and objective response rates (ORR) were significantly improved with nivolumab plus ipilimumab and nivolumab versus ipilimumab in advanced melanoma.

The 4-year analysis presented at ESMO 2018 Congress represents the longest follow-up of a phase III study evaluating checkpoint inhibitor combination therapy.
The median time on treatment was longest with the combination at not reached [NR] compared to 25.2 months with nivolumab and 8.1 months with ipilimumab.
Nivolumab alone or combined with ipilimumab continued to out-perform ipilimumab for both endpoints; median OS was NR (95% confidence interval [CI], 38.2 months-NR) for the combination arm, 36.9 months (95% CI, 28.3-NR) in the nivolumab arm, and 19.9 months (95% CI, 16.9-24.6) with ipilimumab. Median PFS was 11.5 months (95% CI, 8.7-19.3), 6.9 months (95% CI, 5.1-10.2), and 2.9 months (95% CI, 2.8-3.2) for the respective treatment arms. The 4-year OS rates were 53%, and 46%, versus 30% and 4-year PFS rates were 37%, 31%, versus 9% with combination, nivolumab versus ipilimumab treatment, respectively.
The 4-year OS rates were improved further in patients with *BRAF* mutation where median OS with the respective treatments was 62%, 50%, and 30%. Improved 4-year OS rates were also observed in patients with PD-L1 expression levels ≥5% where the 4-year OS rates were 61% with nivolumab plus ipilimumab, 54% with nivolumab, and 36% with ipilimumab. The 4-year rates in patients with *BRAF* wild-type and PD-L1 <5% demonstrated lower OS across all treatment arms. Among patients alive at 4 years, 71%, 50%, and 39% in the combination, nivolumab, and ipilimumab arms, respectively, were treatment-free, no longer receiving study treatment and without subsequent systemic therapy. No new safety signals were observed. NCT01844505. Hodi *et al.* Published simultaneously in the *Lancet Oncology.*[1] Abstract LBA44

Practice point and future research opportunities

This study demonstrated that long-term survival was achieved with nivolumab plus ipilimumab and nivolumab alone in patients with advanced melanoma. Descriptive analyses suggest that higher survival rates are greater with the combination which also yielded a higher proportion of treatment-free patients than nivolumab monotherapy, indicating that

first-line combined nivolumab plus ipilimumab may reduce the need for subsequent therapy or prolong the time to subsequent therapy when needed.

Citation:

1. Hodi FS, Chiarion-Sileni V, Gonzalez R, *et al*. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncology* 2018; 19(11):1480-1492.

Pembrolizumab added to dabrafenib and trametinib improves survival in *BRAF*-mutated advanced melanoma

Paolo A. Ascierto, Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori Fondazione G. Pascale, Napoli, Italy, presented findings on behalf of colleagues from the updated KEYNOTE-022 study which investigated triplet therapy comprising pembrolizumab, dabrafenib, and trametinib in patients with advanced *BRAF*-mutated melanoma. The double-blind part 2 of the phase II KEYNOTE-022 trial randomised treatment naive patients with $BRAF^{V600E/K}$-mutated stage III/IV melanoma; 60 patients in each arm received pembrolizumab at 2 mg/kg every 3 weeks plus dabrafenib at 150 mg twice daily plus trametinib at 2 mg per day, or placebo plus the same regimens of dabrafenib plus trametinib. Patients were stratified by ECOG performance status (0 versus 1) and LDH level (>1.1 versus ≤ 1.1×ULN). The primary endpoint was progression-free survival (PFS) and additional endpoints included objective response rate (ORR), duration of response (DoR), time to recurrence (TTR), and overall survival (OS).

The analysis was done at a median follow-up of 9.6 (range, 2.7 to 23.4) months. Median PFS was 16.0 months (95% confidence interval [CI], 8.6-21.5) with triplet therapy compared to 10.3 months (95% CI 7.0-15.6) with placebo/dabrafenib/trametinib (hazard ratio [HR] 0.66; p = 0.04287). The 12-month PFS rates were 59% versus 45%, respectively. The OS rates at 12 months were 80% with triplet therapy versus 73% with placebo/dabrafenib/trametinib. The ORR was 63% with the triplet compared to 72% with the placebo combination, which included complete response (CR) rates of 18% versus 13%, respectively. Although the median TTR was equal at 2.8 months in both arms, median DoR was 18.7 (range, 1.9+ to 22.1) versus 12.5 (range, 2.1 to 19.5+) with triplet versus control and 60% of patients on pembrolizumab dabrafenib/trametinib demonstrated responses of 18 or more months compared to 28% of patients on placebo/dabrafenib/trametinib.

Any grade treatment-related adverse events (TRAEs) occurred in 95% versus 93% and grade 3 to 5 TRAEs were experienced by 58% versus 27% of patients with triplet versus control. Grade 3 to 5 TRAEs occurring in ≥5% of patients included pyrexia (10% versus 3%), ALT increase (7% versus 5%), AST increase (8% versus 5%), increased GGT (7% versus 5%), rash (5% versus 2%), and neutropaenia (2% versus 5%). Twice as many triplet patients (40% versus 20%) discontinued treatment due to TRAEs, and one treatment related death due to pneumonitis occurred with pembrolizumab, dabrafenib and trametinib. Immune-mediated AEs occurred in 43% versus 13% of patients, most commonly pneumonitis (15%

versus 2%), hypothyroidism (8% versus 2%), skin disorders (7% versus 2%), hyperthyroidism (5% versus 0%), and uveitis (5% versus 3%), respectively. Of these, the majority resolved with treatment discontinuation or modification. NCT02130466. Ascierto *et al.* Abstract 1244O

Practice point and future research opportunities

Long-term results from the KEYNOTE-022 trial indicate that triplet therapy with pembrolizumab, dabrafenib and trametinib demonstrated numerically longer PFS and DoR and a higher rate of grades 3 to 5 TRAEs compared to placebo, dabrafenib and trametinib in patients with treatment-naive $BRAF^{V600E/K}$-mutated advanced melanoma.

NEUROENDOCRINE TUMOURS

Lenvatinib shows promising efficacy in patients with advanced pancreatic and gastrointestinal neuroendocrine tumours

Jaume Capdevila, Gastrointestinal and Endocrine Tumour Unit, Vall d'Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain, and colleagues evaluated lenvatinib efficacy in patients with advanced well-differentiated (G1/G2) neuroendocrine tumours (NETs). Although everolimus and sunitinib are approved in this setting, nether has demonstrated overall response rates (ORR) greater than 10% and no activity with either agent has been demonstrated after progression on prior targeted agents.

The international prospective phase II TALENT trial investigated lenvatinib, a multikinase inhibitor targeting VEGFR1-3 and FGFR1-4, in two cohorts of patients with advanced G1/G2 pancreatic NETs (cohort A) and gastrointestinal NETs (cohort B). All patients demonstrated disease progression (PD) according to RECIST on prior therapies; cohort A patients had PD on everolimus or sunitinib, regardless of prior therapy with somatostatin analogues (SSAs) or chemotherapy and cohort B patients progressed on SSAs. The median age of the patients was 59 years, 51% were male, and 70% were G2. In cohort A, 32% of patients had previously been treated with chemotherapy, 87% with SSAs, 70% with everolimus, and 30% with sunitinib. Fifty-five patients in cohort A and 56 patients in cohort B received lenvatinib at 24 mg daily until PD or intolerable toxicity. The primary endpoint was objective response rate (ORR) by RECIST v1.1 upon central radiology review.

The ORR in the overall study was 29%, which broke down to 40% in pancreatic NETs patients and 18.5% for patients with gastrointestinal NETs; stable disease was the best response in 55.7% and 76% of patients, respectively. After a median follow-up of 11 months, the estimated median progression-free survival was 14.2 months (95% confidence interval [CI], 11.4-not reached [NR]) and 17.6 months (95% CI, 11.5-NR) months in cohorts A and B, respectively. Adverse events (AEs) that occurred in 90% of patients included fatigue, diarrhoea, and hypertension. Grade 3/4 AEs were reported in 10% of patients. Lenvatinib showed significant anti-tumour activity and a favourable toxicity profile in progressive advanced NETs. NCT02678780. Capdevila *et al.* Abstract 1307O

Practice point and future research opportunities

In this phase II trial, lenvatinib showed anti-tumour activity in patients with advanced pancreatic and gastrointestinal NETs, which are populations with a high medical need for new treatments. The highest reported response in this population of pre-treated patients was demonstrated with lenvatinib in patients with pancreatic NETs, which warrants further study.

Spartalizumab (PDR001) shows encouraging activity in patients with advanced neuroendocrine tumours of thoracic origin, who have progressed on prior treatment

James C. Yao, Department of Gastrointestinal Medical Oncology, University of Texas/MD Anderson Cancer Centre, Houston, USA and a research team evaluated the efficacy and safety of spartalizumab (PDR001) in this phase II, multicentre study in patients with non-functional well- and poorly-differentiated neuroendocrine tumours (NETs). Spartalizumab is a high-affinity, humanised, anti-PD-1 IgG4 antibody that blocks binding of both PD-L1 and PD-L2 to PD-1.

The trial enrolled 33 patients with pancreatic NETs, 32 with gastrointestinal advanced NETs, and 30 patients with thoracic advanced NETs as well as 21 patients with gastroenteropancreatic neuroendocrine carcinoma (GEP NEC). All patients with NETs had progressed on prior treatments including everolimus, while GEP NEC patients progressed on one line of chemotherapy. Enrolment was regardless of PD-L1 expression. The primary endpoint was overall response rate (ORR) by central review and secondary endpoints included duration of response (DoR), biomarker analyses, and safety. Spartalizumab was administered at 400 mg, every 4 weeks via 30 min i.v. infusion until disease progression or unacceptable toxicity occurred.

The preliminary results in the data snapshot presented at ESMO 2018 were evaluated after a median follow-up of 7.6 months in NET and 6 months in GEP NEC patients. In pooled data from patients with well-differentiated NET, the ORR was 7.4% and 4.8% in patients with poorly-diff GEP NEC. The highest response according to disease type was observed in patients with thoracic NET where a 20% partial response (PR) rate was demonstrated, and 53.3% of patients achieved stable disease (SD) for a disease control rate (DCR) of 73.3% (10% of patients had unknown outcomes as of the date of analysis). Clinical activity was marginal in the other cohorts: Patients with pancreatic NETs had a PR rate of 3.0% and 54.5 SD for a DCR of 57.6 (3.0% unknown). In patients with gastrointestinal NETs, 59.4% of patients demonstrated SD (DCR 59.4; 6.3% unknown). In the GEP NEC population, 4.8% of patients had PR, 14.4% had SD and the DCR was 19.0% (14.3% unknown). The most common grade 3/4 all cause adverse events that occurred in >25% of patients were abdominal and back pain, anaemia, dyspnoea, and hypertension.

PD-L1 testing showed that PD-L1 expression was generally low; patients with GEP NEC showed a higher proportion of PD-L1 expression <1% in immune cells of 43% versus 19% in thoracic NETs, 23% in pancreatic NETs, and 10% in patients with gastrointestinal NETs. The results from the biomarker analysis suggested a potential link between TIM-3 expression and lack of response to treatment. NCT02955069. Yao *et al.* Abstract 1308O

Practice point and future research opportunities

These preliminary results suggest novel spartalizumab has clinical activity in patients with well-differentiated non-functional NETs of thoracic origin. Further studies are needed to explore the role of immunotherapy combinations, identifying predictive biomarkers for immuno-oncology response, and for strategies to increase the immunotherapy response in the population of patients with difficult to treat NET and GEP NEC.

NSCLC

Erlotinib demonstrates stronger activity than gemcitabine plus cisplatin as neo-adjuvant therapy in patients with NSCLC and *EGFR* mutation

Lead author Wen-Zhao Zhong, Guangdong Lung Cancer Institute, in Guangzhou, China presented findings from the CTONG 1103 study of erlotinib compared to gemcitabine plus cisplatin chemotherapy in the neoadjuvant/adjuvant setting in patients with stage IIIA-N2 *EGFR* mutated non-small cell lung cancer (NSCLC). Of the 386 patients from 17 centres in China who were screened, 72 patients comprised the intent-to-treat (ITT) population that was randomised equally to receive erlotinib for 42 days as neoadjuvant therapy followed by 12 months of post-surgical erlotinib or to receive neoadjuvant therapy for 2 cycles and 2 cycles of post-surgical gemcitabine plus cisplatin. The objective response rate (ORR) served as the primary endpoint and secondary endpoints included downstaging rates of pathological lymph nodes, pathological complete response (pCR), progression-free survival (PFS), overall survival (OS), safety, and tolerability.

The study met the primary endpoint, demonstrating an ORR of 54.2% (95% confidence interval [CI], 37.2%-70.9%) with neoadjuvant erlotinib versus 34.3% (95% CI, 17.7%-50.8%) with gemcitabine plus cisplatin, OR 2.26 (95% CI, 0.87–5.84; p = 0.092). A major pathological response (MPR) was observed only in 3 (10.7%) of the patients receiving erlotinib. Following neoadjuvant therapy, 83.8% of patients in the erlotinib group and 68.6% in the gemcitabine plus cisplatin group underwent surgery. Lymph node downstaging was possible in 13% of erlotinib patients compared to 4.2% of patients receiving gemcitabine/cisplatin. Median PFS was significantly longer with erlotinib at 21.5 months (95% CI, 19.3-23.6) versus 11.9 months (95% CI, 9.1-14.7) with gemcitabine/cisplatin (hazard ratio 0.42; 95% CI, 0.23-0.76; p = 0.0003). The OS data were immature. No grade 3 and 4 toxicities (0%) were reported in the erlotinib arm compared to 29.4% in the gemcitabine plus cisplatin arm. NCT01407822. Zhong *et al.* Abstract LBA48_PR

Practice point and future research opportunities

Neoadjuvant/adjuvant erlotinib improved response, and significantly prolonged PFS compared with gemcitabine plus cisplatin chemotherapy in patients with stage IIIA-N2 *EGFR* mutated NSCLC. Neoadjuvant erlotinib also allowed for a greater degree of lymph node downstaging prior to surgery and showed no grade 3/4 toxicities.

This randomised study is the first to demonstrate improvement in multiple parameters including tumour response rate, resection rate, major pathologic response, and PFS with the use of neoadjuvant an EGFR tyrosine kinase inhibitor (TKI) followed by an adjuvant TKI. While the difference between EGFR TKI and chemotherapy is significant, the impact of neoadjuvant EGFR TKI is relatively disappointing. The response rate of 54% is lower than the approximately 70% expected rate for TKI in stage IV disease, and only 13% of patients had attained major pathologic response. The reason for this is unclear, but one may have

to query if the duration of neoadjuvant EGFR TKI for 42 days is sufficient. Overall, this important study offers the rationale to consider neoadjuvant EGFR TKI.

Neoadjuvant nivolumab and nivolumab plus ipilimumab provide encouraging responses and are well tolerated in resectable NSCLC

Tina Cascone, Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Centre, Houston, USA, and fellow investigators evaluated whether peri-operative immunotherapy in early-stage, resectable non-small cell lung cancer (NSCLC) can offer a survival benefit, given that 30 to 60% of patients with stage I-III NSCLC ultimately develop metastasis post-resection. At ESMO 2018, preliminary results of the NEOSTAR phase II trial of neoadjuvant nivolumab or nivolumab plus ipilimumab in patients with stage I-IIIA (single N2) resectable NSCLC and ECOG performance status 0-1 were reported. NEOSTAR randomly assigned patients to nivolumab at 3 mg/kg i.v. every 2 weeks, on days 1, 15, and 29 or to combined nivolumab (same regimen) plus ipilimumab at 1 mg/kg i.v. on day 1 followed by surgery. Of the 33 patients randomised, 17 received nivolumab and 16 received combination nivolumab/ipilimumab therapy. Their mean age was 65 years, 67% were male, 21% were never smokers, and 58% of the patients had adenocarcinoma. Stage I, II, and III disease was reported in 10, 15, and 8 patients, respectively. The primary endpoint was major pathologic response (MPR), which was defined as ≤10% viable tumour cells at surgery. Immune infiltrates were assessed by flow cytometry on checkpoint inhibitor (CPI)-treated tumours and compared to untreated resected samples (ICON set).

Of the 30 patients completing neoadjuvant therapy, 18 patients on nivolumab and 26 on nivolumab/ipilimumab had surgery; 5 patients were unresectable, and 2 resections are pending. Surgical complications included one bronchopleural fistula (BPF). The median percent of viable tumour cells was lower in post nivolumab/ipilimumab patients than post nivolumab, 28% versus 65% ($p = 0.32$). The overall MPR rate in 31 patients was 26%; the MPR rate with nivolumab was 25% and 27% with nivolumab/ipilimumab. Overall 5 pathologic complete responses (pCR) were observed; of these 2 were in the nivolumab arm and 3 were in the combination arm. The radiographic objective response rate (ORR) by RECIST v1.1 was 19%, which included 5 partial responses with nivolumab and one complete response with nivolumab plus ipilimumab. Progressive disease occurred in 19% of patients, 3 patients per treatment arm. Treatment-related adverse events (TRAEs) included one grade 5 death due to BPF post steroid-treated pneumonitis in the nivolumab arm; grade 3 pneumonia and hypoxia occurred in one patient each receiving nivolumab. Grade 2 cough was seen in 3 patients on nivolumab/ipilimumab and one patient each in the nivolumab arm reported grade 2 rash and fatigue.

In the ICON analysis, the immunotherapies increased proliferative (Ki67+) and activated (ICOS+) effector CD8+ & CD4+ tumour infiltrating lymphocytes (TILs) in the treated tumour samples compared to untreated tumours ($p<0.0001$). CD27+CD28+ effector memory and CD8+ TILs were higher (49%) with nivolumab versus 33% with nivolumab/ipilimumab ($p = 0.06$), as were Ki67+CD103+ tissue resident effector CD8+ cells, (98% versus 65%,

respectively; p = 0.1) and CD4+ cells (99% versus 40%, p = 0.03). By contrast, TILs and Tregs were higher with the combination treatment versus nivolumab (97% versus 47%, p = 0.06). NCT03158129. Cascone *et al.* Abstract LBA49

Practice point and future research opportunities

These results indicate that distinct anti-tumour immune responses may be triggered by the neoadjuvant checkpoint inhibitor regimen. Patients treated with the combination showed significantly higher proliferation of distinct, T-cell subsets than those receiving monotherapy. Both regimens were generally well tolerated. Currently, there are several trials evaluating neoadjuvant checkpoint blockade in early NSCLC and their results are eagerly awaited to supplement these encouraging data.

Mechanisms of acquired resistance to first-line osimertinib are detected using patient samples from the phase III FLAURA study

Suresh S. Ramalingam, Department of Haematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, USA presented preliminary data describing the mechanisms of acquired resistance to osimertinib in patients who progressed during the phase III FLAURA study. In FLAURA, osimertinib showed superior efficacy compared with standard of care (SoC) epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with previously untreated EGFR mutated advanced non-small cell lung cancer (NSCLC). The trial randomised 556 patients with previously untreated advanced NSCLC and EGFR mutation in ex19del/L858R: 279 patients were assigned to osimertinib at 80 mg once daily and 277 to SoC EGFR-TKI consisting of gefitinib at 250 mg once daily or erlotinib at 150 mg once daily. Paired plasma samples were collected at baseline and upon progression and/or treatment discontinuation. Plasma samples were analysed using next generation sequencing (NGS; Guardant Health; Guardant360 73 gene panel or Omni 500 gene panel). Disease progression or treatment discontinuation had occurred in 41% of patients on osimertinib and 57% of patients on SoC EGFR-TKI. Of these patients with paired plasma samples, only patients with detectable plasma EGFR mutation (ex19del/L858R) at baseline were evaluable for this analysis, which consisted of 81% of patients in each treatment arm.

No evidence of acquired EGFR T790M was detected by NGS in samples for patients in the osimertinib arm, where the most common acquired resistance mechanism detected was MET amplification in 15% of patients, followed by EGFR C797S mutation in 7% of patients. Other resistance mechanisms included HER2 amplification, PIK3CA and RAS mutations, which occurred in 2 to 7% of samples. In the SoC arm, the most common resistance mechanisms were T790M mutation in 47% of patients, MET amplification in 4%, and HER2 amplification in 2% of patients. Further investigation of novel acquired mutations is ongoing. NCT02296125. Ramalingam *et al.* Abstract LBA50

Practice point and future research opportunities

This analysis of paired samples obtained from patients having detectable baseline plasma EGFR mutation and who experienced disease progression and/or discontinued treatment revealed heterogeneous resistance mechanisms. With first-line osimertinib, the most commonly detected resistence mechanisms detected were MET amplification and EGFR C797S mutation. Approximately 50% of SoC-treated patients acquired T790M, which is in accord with previous analyses. None of the osimertinib-treated patients acquired T790M, and no unexpected resistance mechanisms were observed in this cohort. This and other analyses of resistance should inform treatment decisions in patients experiencing disease progression or recurrence.

Analysis of resistance mechanisms to osimertinib in patients with EGFR T790M advanced NSCLC participating in the AURA3 study

Vassiliki A. Papadimitrakopoulou, MD Anderson Cancer Centre in Houston, USA and colleagues analysed samples obtained from patients participating in the phase III AURA3 trial to determine resistance mechanisms to osimertinib. In AURA3, osimertinib demonstrated superior efficacy compared with platinum-based doublet chemotherapy in patients with T790M-positive advanced non-small cell lung cancer (NSCLC), whose disease progressed during or after treatment with a first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Patients with EGFR T790M advanced NSCLC and disease progression were randomised 2:1 to receive osimertinib at 80 mg once daily or platinum-based doublet chemotherapy. Paired plasma samples were collected at baseline and at the time of disease progression and/or treatment discontinuation. Plasma samples were analysed by next generation sequencing (NGS; Guardant Health, Guardant360, 73 gene panel).

Of 279 patients randomised to the osimertinib treatment arm, paired plasma samples were available from 83 (30%) patients who had progressed and/or discontinued treatment. Of this cohort, 73 (88%) patients had baseline detectable ctDNA EGFR mutations, consisting of either L858R, exon 19 deletion or T790M and were evaluable in this analysis. No T790M mutations were detected in 36 (49%) patients at progression or discontinuation and 11 (15%) patients acquired EGFR secondary mutation in C797 (C797S n=10; C797G n=1) at this timepoint. Amplifications of MET, HER2, and PIK3CA were detected in 14 (19%), 4 (5%), and 3 (4%) samples, respectively. Other mechanisms of acquired resistance included 3 (4%) samples with mutations in BRAF V600E, one (1%) sample each with mutated KRAS and PIK3CA E545K. The analysis also detected 3 (4%) oncogenic fusion mutations in FGFR3, RET and NTRK. NCT02151981. Papadimitrakopoulou *et al.* Abstract LBA51

Practice point and future research opportunities

This preliminary analysis of paired plasma samples obtained from patients with detectable baseline plasma EGFR mutations at disease progression and/or treatment discontinuation

showed a diverse mixture of resistance mechanisms. Patients most often displayed MET amplification and EGFR C797S, and no unexpected resistance mechanisms were observed in these patients treated with second-line osimertinib. This study adds to the understanding of resistance mechanisms in the first and second-line settings, which will help define appropriate combination therapies for further treatment of these patients.

Capmatinib is highly active in patients with MetΔex14-mutated NSCLC

Juergen Wolf of the Centre for Integrated Oncology, University Hospital Cologne in Cologne, Germany presented findings on behalf of colleagues from the phase II GEOMETRY mono-1 study, which assessed the response to treatment with capmatinib in both pre-treated and treatment naive patients with advanced non-small cell lung cancer (NSCLC) and *METΔex14* mutations. Capmatinib demonstrated strong clinical benefit with nearly three-fourths of patients who were previously untreated for *METΔex14* mutated advanced NSCLC showing a response following 4 months of oral capmatinib. Patients who had received prior treatment for advanced *METΔex14* mutated NSCLC also demonstrated a response to capmatinib, a novel, orally available, highly potent and selective inhibitor of MET. MET plays a key role in tumour cell proliferation, survival, invasion, metastasis, as well as tumour angiogenesis. MET mutations leading to exon 14 deletion (*MET*Δex14) have been observed in approximately 3% to 4% of patients with NSCLC.

Professor Wolf reported the results of cohorts 4 and 5b of the GEOMETRY study. Both cohorts comprised patients with centrally confirmed *MET*Δex14 mutated or MET amplified advanced NSCLC; cohort 4 patients had received 1 to 2 prior lines of therapy and cohort 5b patients were treatment-naive. All patients were ≥18 years of age, with ECOG performance status 0 or 1 and had *ALK* and *EGFR* wild-type, stage IIIB/IV NSCLC of any histology. The patients were treated with capmatinib tablets at 400 mg twice daily.

The primary endpoint was overall response rate (ORR) by blinded independent central review (BIRC) per RECIST v1.1. The key secondary endpoint was duration of response (DoR) by BIRC.

At a follow-up of 18 weeks or more, 69 cohort 4 and 25 cohort 5b patients had available data and were included in the analysis. Treatment naive patients demonstrated a greater response to capmatinib; the confirmed ORR was 39.1% (95% confidence interval [CI], 27.6-51.6) in previously treated cohort 4 patients, and 72.0% (95% CI, 50.6-87.9) in treatment naive cohort 5b patients. At this time, treatment was ongoing for 20.3% of cohort 4 patients and 44.0% of cohort 5b patients.

Preliminary activity in patients with brain metastases was also observed. At a median follow-up of 5.6 months, DoR data were not mature. The most frequently reported adverse events (AEs) of any grade irrespective of causality occurring in ≥ 20% of the 302 patients across all six cohorts of the trial included peripheral oedema in 49.0% of patients, nausea in 43.4%, vomiting in 28.5%, blood creatinine increased in 24.5%, and dyspnoea in 24.2% of patients.

Decreased appetite (21.2%) and fatigue (20.9%) were also reported in 21.2% and 20.9% of patients, respectively. Most of the AEs were grades 1/2. Wolf *et al.* Abstract LBA52

Practice point and future research opportunities

Capmatinib treatment demonstrated a clinically meaningful ORR rate of 72% by BIRC in treatment naive patients with NSCLC and *MET*Δex14 mutation, which constitutes a challenging patient population. Capmatinib also demonstrated a manageable toxicity profile. The differential benefit that was observed between patients receiving capmatinib as first-line and as second-line and beyond, suggests a need for earlier diagnostic testing and prompt first-line treatment for optimal capmatinib benefit.

Health-related quality of life is improved with pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel in patients with metastatic squamous NSCLC: data from KEYNOTE-407

Julien Mazieres, Centre Hospitalier, Universitaire de Toulouse, Toulouse, France, presented health-related quality of life (HRQoL) on behalf of the KEYNOTE-407 investigators. The randomised, double-blind, phase III KEYNOTE-407 trial demonstrated improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) with pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel compared with placebo plus carboplatin and paclitaxel or nab-paclitaxel as first-line therapy for patients with metastatic squamous non-small cell lung cancer (NSCLC). The trial included HRQoL, as evaluated by patient-reported outcomes (PROs) as a prespecified exploratory endpoint. In KEYNOTE-407, 559 patients with previously untreated stage IV squamous NSCLC, ECOG performance status 0–1, and measurable disease per RECIST v1.1 were randomised 1:1 to receive 4 cycles of pembrolizumab at 200 mg every 3 weeks or placebo plus carboplatin every 3 weeks at AUC 6, paclitaxel at 200 mg/m^2 every 3 weeks or nab-paclitaxel at 100 mg/m^2 weekly, followed by pembrolizumab or placebo for up to 35 cycles total. The EORTC QLQ-C30 and QLQ-LC13 questionnaires were administered at cycles 1–7, then every 3 cycles up to week 48. Prespecified key PROs included change from baseline to weeks 9 and 18 in the QLQ-C30 global health status (GHS/QoL) score and the time to 10-point deterioration in the composite endpoint for cough, chest pain, or dyspnoea. The PRO analyses included 554 and 553 patients who completed ≥1 QLQ-C30 or ≥1 QLQ-LC13 assessment, respectively, and received ≥1 administration of study treatment.

The mean QLQ-C30 GHS/QoL baseline scores were similar in the pembrolizumab combination and placebo combination arms at 63.9 and 62.7, as were compliance rates of approximately 94%, 84%, and 87% at baseline, week 9, and week 18, respectively. The QLQ-C30 GHS/QoL scores improved from baseline at weeks 9 and 18, whereas the placebo arm showed a decrease in mean scores; the least squares mean difference (LSMD) between groups at week 9 was 3.6 points (95% confidence interval [CI], 0.3-6.9; p = 0.0337), and at week 18 the LSMD was 4.9 points (95% CI, 1.4-8.3; p = 0.0060). The median time to deterioration in the composite endpoint of cough, chest pain, or dyspnoea was not

reached in either arm (hazard ratio 0.79; 95% CI, 0.58-1.06; p = 0.125). NCT02775435. Mazieres *et al.* Abstract LBA62

Practice point and future research opportunities

HRQoL findings from KEYNOTE-407 demonstrate that adding pembrolizumab to chemotherapy maintained or improved HRQoL measurements compared to chemotherapy, and further support the pembrolizumab plus chemotherapy regimen as first-line therapy for patients with metastatic squamous NSCLC.

Front-line atezolizumab added to chemotherapy improves survival over chemotherapy in advanced non-squamous NSCLC

Federico Cappuzzo, Dipartimento di Oncologia Medica, Azienda Unità Sanitaria Locale della Romagna in Ravenna, Italy, discussed findings from the phase III, multicentre, open-label, randomised IMpower130 trial, which evaluated the efficacy and safety of atezolizumab in combination with carboplatin and nab-paclitaxel versus carboplatin and nab-paclitaxel chemotherapy in the first-line setting for patients with stage measurable (RECIST) IV non-squamous non-small cell lung cancer (NSCLC).
The study randomised 724 patients 2:1 to receive carboplatin AUC 6 every 3 weeks, and nab-paclitaxel at 100 mg/m^2 i.v. per week, with or without atezolizumab at 1200 mg i.v. every 3 weeks. Patients on chemotherapy also received best supportive care and pemetrexed every 3 weeks as maintenance until disease progression, whereas patients in the atezolizumab arm received atezolizumab maintenance until loss of clinical benefit. Crossover to atezolizumab upon disease progression (PD) was permitted. The co-primary endpoints of the trial were investigator-assessed progression-free survival (PFS) and overall survival (OS) in the intent-to-treat (ITT) wild -type (wt) and in the *EGFR*-wt/*ALK*-negative populations. Secondary endpoints included OS and PFS in the ITT population and according to PD-L1 expression, response rate and safety.

This analysis included 723 ITT and 679 ITT-wt patients and revealed statistically significant, clinically meaningful improvements in OS and PFS in both populations with the atezolizumab combination. In the ITT-wt population median OS was 18.6 months (95% confidence interval [CI], 16.0-21.2) in 451 patients on atezolizumab compared to 13.9 months (95% CI, 12.0-18.7) in 228 patients receiving chemotherapy (hazard ratio [HR] 0.79, 95% CI, 0.64-0.98; p = 0.033) and the 12-month OS rates were 63.1% versus 55.5%, respectively. Median PFS in the ITT-wt population was 7 months (95% CI, 6.2-7.3) versus 5.5 months (95% CI, 4.4-5.9) with atezolizumab versus chemotherapy (HR 0.64, 95% CI, 0.54-0.77; p < 0.0001) and the 12-month PFS rates were 29.1% versus 14.1%, respectively. In 447 patients receiving the atezolizumab combination versus 225 patients on chemotherapy, confirmed objective response rate (ORR) rates were 49.2% versus 31.9% and the median duration of response (DoR) rates in responding patients were 8.4 months versus 6.1 months, respectively.

In the ITT population, 483 patients receiving the atezolizumab combination versus 240 patients receiving chemotherapy showed median OS of 18.1 (95% CI, 15.3-20.8) versus 13.9 (95% CI, 12.0-18.2) months (HR 0.80, 95% CI, 0.65-0.99; p = 0.039) and median PFS of 7.0 (95% CI, 6.3-7.3) versus 5.6 (95% CI, 4.5-5.9) months (HR 0.65, 95% CI, 0.54-0.77; p < 0.0001).

The PFS and OS benefit with atezolizumab was observed across all PD-L1 subgroups; in the PD-L1 high subgroup 88 patients receiving the atezolizumab combination had median OS of 17.4 months (95% CI, 14.78-not available [NA]) compared to 16.9 months (95% CI, 10.94-NA) in 42 patients receiving chemotherapy (HR 0.84, 95% CI, 0.51-1.39), and median PFS was 6.4 months (95% CI, 5.49-9.76) compared to 4.6 months (95% CI, 3.22-7) with atezolizumab versus chemotherapy (HR 0.51, 95% CI, 0.34-0.77).

Patients in the PD-L1 low subgroup receiving atezolizumab (n=128) versus chemotherapy (n=121) had median OS of 23.7 (95% CI, 18.63-NA) versus 15.9 months (95% CI, 12.32-25.63), respectively (HR 0.70, 95% CI, 0.45-1.08), and median PFS was 8.3 months (95% CI, 7.0 (6.2-7.3) versus 6.0 months (95% CI, 5.29-6.93) respectively (HR 0.61, 95% CI, 0.43-0.85). The poorest survival was seen in the PD-L1 negative subgroup, where patients on atezolizumab (n=235) versus chemotherapy (n= 121) demonstrated median OS of 15.2 (95% CI, 12.88-19.15) versus 12.0 (95% CI, 8.97-17.71) months (HR 0.81; 95% CI, 0.61-1.08), and median PFS of 6.2 (95% CI, 5.52-7.16) versus 4.7 (95% CI, 4.11-5.72) months (HR 0.72; 95% CI, 0.56-0.91).

Improved clinical benefit with atezolizumab was observed across all populations, except subgroups of patients with liver metastases and EGFR/ALK genomic alterations. With atezolizumab, 73.2% versus 60.3% of patients on chemotherapy had grade 3/4 treatment-related adverse events. No new safety signals were identified. NCT02367781. Cappuzzo *et al.* Abstract LBA53

Practice point and future research opportunities

IMpower130 showed statistically significant, clinically meaningful improvements in OS and PFS with atezolizumab in combination with carboplatin and nab-paclitaxel compared to carboplatin and nab-paclitaxel chemotherapy in stage IV non-squamous NSCLC, irrespective of PD-L1 expression.

Adding atezolizumab to carboplatin/cisplatin plus pemetrexed improves survival across key subgroups with stage IV non-squamous NSCLC

Fabrice Barlesi, Assistance Publique Hôpitaux de Marseille, Aix Marseille Université, Marseille, France, and colleagues conducted the global phase III IMpower132 study to evaluate whether the addition of atezolizumab to platinum-based pemetrexed combinations in the first-line setting improved clinical benefit in patients with metastatic non-squamous non-small cell lung cancer (NSCLC), whose tumours did not contain sensitising EGFR or

ALK mutations. The investigators randomly assigned 292 patients to 4 or 6 cycles of either atezolizumab at 1200 mg plus carboplatin at AUC 6 or cisplatin at 75 mg/m^2 plus pemetrexed at 500 mg/m^2 and 286 patients to carboplatin at AUC 6 or cisplatin at 75 mg/m^2 plus pemetrexed at 500 mg/m^2, followed by maintenance therapy with atezolizumab at 1200 mg plus pemetrexed at 500 mg/m^2 or pemetrexed at 500 mg/m^2 alone. Atezolizumab maintenance could be continued beyond disease progression. All patients were treatment naive. Exploratory efficacy analyses were performed to assess the clinical benefit across key subgroups, including smoking status, liver metastasis ethnicity, and age. The co-primary endpoints were progression-free survival (PFS) and overall survival (OS) in the intent-to-treat (ITT) population.

IMpower132 met its co-primary endpoint of PFS in the ITT population and demonstrated a numerical advantage in OS across all cohorts. Median PFS was 7.6 months (95% confidence interval [CI], 6.6-8.5) with the atezolizumab combination compared to 5.2 months (95% CI, 4.3-5.6) with chemotherapy (hazard ratio [HR] 0.59; 95% CI, 0.494-0.719; p = 0.0001). Median OS was 18.1 months (95% CI, 13.0-not estimated [NE]) with the atezolizumab combination versus 13.6 months (95% CI, 11.4-15.5) with carboplatin/cisplatin (HR 0.813; 95% CI, 0.644-1.025; p = 0.0797).

Subgroup analysis showed that PFS was improved with atezolizumab versus chemotherapy, especially in Asian patients compared to non-Asian; median PFS was 10.2 versus 5.3 months (HR 0.42; 95% CI, 0.028-0.63) in Asian and 6.9 versus 5.0 months in non-Asian patients (HR 0.65; 95% CI, 0.53-0.81) with the respective treatments. Median OS was NE with the atezolizumab combination versus NE with carboplatin/cisplatin (HR 0.68; 95% CI, 0.37-1.24) in Asian patients compared to 13.0 versus 11.0 months (HR 0.82; 95% CI, 0.64-1.06) in non-Asian patients, respectively.

Patients ≥ 65 years fared better than patients <65 years regarding PFS; median PFS was 8.4 versus 5.6 months (HR 0.55; 95% CI, 0.42-0.73) in older patients compared to 6.9 versus 4.4 months (HR 0.63; 95% CI, 0.49-0.80) in younger patients, with the atezolizumab combination versus chemotherapy. Median OS in older patients was 18.1 months with the atezolizumab combination versus 12.8 months with carboplatin/cisplatin and pemetrexed (HR 0.71; 95% CI, 0.50-1.01) compared to 18.8 months versus 12.8 months (HR 0.89; 95% CI, 0.62-1.21) in patients aged <65 years, respectively.

Median PFS with the respective treatments in never smokers was 8.6 versus 5.5 months (HR 0.49; 95% CI, 0.28-0.87) compared to 7.5 versus 5.1 months (HR 0.61; 95% CI, 0.50-0.74) in former or current smokers. Median OS in never-smokers was 18.1 versus 13.3 months (HR 0.65; 95% CI, 0.32-1.30) compared to 18.8 versus 13.6 months (HR 0.83; 95% CI, 0.65-1.06) in former or current smokers, respectively.

Median PFS with atezolizumab compared to chemotherapy in patients without liver metastasis was 8.4 versus 5.5 months (HR 0.56; 95% CI, 0.46-0.69) compared to 4.4 versus 4.0 months (HR 0.77; 95% CI, 0.47-1.25) in patients with liver metastasis. Median OS in patients without liver metastasis was 19.9 versus 14.2 months (HR 0.76; 95% CI, 0.59-0.98)

compared to 10.1 versus 6.9 months (HR 0.99; 95% CI, 0.57-1.70) in patients with liver metastasis in the atezolizumab versus carboplatin/cisplatin plus pemetrexed arms, respectively. NCT02657434. Barlesi *et al.* LBA54

Practice point and future research opportunities

The addition of atezolizumab to carboplatin or cisplatin plus pemetrexed resulted in improved PFS and OS in the ITT population and across key clinical subgroups. The survival benefit appeared to be more pronounced in Asian patients, older patients, and never smokers. Further analyses may provide new insights into the mechanisms underlying these effects and may improve future treatment options for patients with metastatic non-squamous NSCLC and no sensitising mutation.

B-F1RST study finds blood-based tumour mutational burden as a biomarker of atezolizumab activity in first-line NSCLC

Edward Kim, Department of Solid Tumour Oncology and Investigational Therapeutics, Levine Cancer Institute, Atrium Health, Carolinas HealthCare System in Charlotte, USA, presented primary efficacy results from the prospective phase II B-F1RST trial. BF1RST evaluated the utility of a novel blood-based tumour mutational burden (TMB) assay as a predictive biomarker for atezolizumab when administered as first-line therapy to PD-L1–unselected patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). He pointed out that approximately 30% of patients with NSCLC have inadequate tumour tissue for molecular testing at diagnosis, therefore, blood-based TMB is being explored as a biomarker. The B-FIRST study also assessed the predictive value of TMB for patients being treated with checkpoint inhibitors. Previously, authors have reported on the retrospective analyses from the randomised, phase III OAK and phase II POPLAR studies wherein the TMB detected in blood and tissue showed promise in predicting benefit from atezolizumab administered as second-line therapy in patients with NSCLC.

The study enrolled 152 patients who comprised the intent-to-treat (ITT) population and received intravenous atezolizumab at 1200 mg every 3 weeks until disease progression or loss of clinical benefit. Of this group, 119 patients were included in the biomarker evaluable population (BEP). Atezolizumab clinical efficacy was assessed according to a prespecified blood TMB cut-off set at ≥ 16, depicting high TMB, or < 16, which was considered low TMB. The co-primary endpoints were objective response rate (ORR) and progression-free survival (PFS).

PD-L1 unselected patients with high levels of blood TMB demonstrated higher response rates and improved survival following first-line atezolizumab monotherapy. At a minimum follow-up of 6 months, the ORR in the overall ITT population was 14.5% and the ORR in the BEP population was 10.1%. In the non-BEP cohort, which had favourable prognostic characteristics, the ORR was 34.5%.

In the ITT population, 119 patients had adequate circulating tumour (ct)DNA, at a maximum somatic allele frequency (MSAF) ≥ 1% and were included in the BEP. Twenty-nine patients had inadequate ctDNA tumour shedding into the blood (MSAF < 1%) and comprised the non-BEP population. At the prespecified blood TMB cut-off ≥16, assessment of the response to atezolizumab in patients with high (≥16) versus low (<16) blood TMB revealed an ORR of 28.6% compared to 4.4%. For PFS, TMB low patients demonstrated median PFS of 3.7 months compared to 4.6 months in patients with high blood TMB (hazard ratio [HR] 0.66; 90% confidence interval [CI], 0.42-1.02). Median overall survival (OS) was not estimable (NE) in patients with blood TMB high compared to 13.1 months in blood TMB low patients (HR 0.77; 90% CI, 0.41-1.43; p = 0.48).

At increasing blood TMB cut-offs ranging from 10 to 20, the hazard ratio for PFS improved from HR 1.09 (blood TMB ≥10) to 0.48 (blood TMB ≥20), emphasizing the proportional relationship between increasing blood TMB score and improved clinical outcomes. Follow-up will continue for ≥18 months, per protocol. In the ITT population, treatment-related serious adverse events (AEs) occurred in 13% of patients and 20% of patients had treatment-related grade 3/4 AEs. Adverse events led to atezolizumab treatment discontinuation in 15% of patients. NCT02848651. Kim *et al.* Abstract LBA55

Practice point and future research opportunities

The B-F1RST primary analysis represents the first prospective dataset evaluating the clinical utility of blood TMB as a predictive biomarker for first-line atezolizumab monotherapy in patients with advanced lung cancer. At the prespecified blood TMB ≥16 cut-off, patients showed numerical benefit for PFS, ORR and OS, which was consistent with interim data. The role of liquid biopsy might be a key factor. B-F1RST has major findings but blood TMB may not capture the more sensitive tumours.

Overall survival is improved with ceritinib in ALK inhibitor-naive patients with ALK-rearranged NSCLC

Enriqueta Felip, Oncology Service, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain, and colleagues conducted the ASCEND-3, single-arm, open-label, multicentre, phase II study evaluating the efficacy and safety of ceritinib in ALK inhibitor-naive patients. At the time of presentation, 124 patients aged, ≥18 years with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who had not received prior ALK inhibitor had enrolled worldwide. All patients were fasted and subsequently treated with oral ceritinib at 750 mg per day. Of these patients, 99.2% had received prior antineoplastic regimens, 25.0% had received ≥3 regimens, and 39.5% had baseline brain metastases. The investigators assessed whole body (WB) and intracranial (IC) responses to ceritinib. The primary endpoint was investigator-assessed overall response rate (ORR) per RECIST v1.1 and secondary endpoints included ORR by blinded independent review committee (BIRC), overall intracranial response rate (OIRR), duration

of response (DoR), disease control rate (DCR), progression-free survival (PFS; by investigator and BIRC), overall survival (OS), and safety.

The median follow-up was 52.14 (range, 48.4 to 60.1) months and the median duration of drug exposure was 23.2 (range, 0.1 to 55.2) months. The study met the primary endpoint; the investigator assessed ORR was 67.7% (95% confidence interval [CI], 58.8-75.9) and the ORR by BIRC was 63.7% (95% CI, 54.6-72.2). In 84 and 79 responding patients by investigator and BIRC, respectively, the median DoR was 24.0 (95% CI, 14.8-37.5) and 27.3 (95% CI, 16.6-44.3) months. The DCR was 90.3% (95% CI, 83.7-94.9) and 86.3% (95% CI, 79.0-91.8) in the respective assessments. Median OS was 51.3 months (95% CI, 42.7-55.3), and median PFS was 16.6 (95% CI, 11.0-23.2) and 19.4 (95% CI, 10.9-29.3).

Overall, the safety profile was consistent with the previous studies. The most common all grade adverse events (AEs) occurring in ≥60% of patients that were suspected of being drug related included (83.1%), nausea (76.6%), and vomiting (69.4%). Grade 3/4 AEs suspected to be drug related were reported in 81 (65.3%) patients and 14.5% of patients discontinued treatment due to an AE. NCT01685138. Felip et al. Abstract LBA57

Practice point and future research opportunities

Ceritinib, a second-generation, oral ALK inhibitor, demonstrated clinical activity in advanced ALK inhibitor-naive patients with ALK positive NSCLC, including those with brain metastases. These findings from the ASCEND-3 study confirm the previously reported results from this study.

Robust intracranial efficacy demonstrated with brigatinib in the phase III ALTA-1L trial

Sanjay Popat, Medical Oncology, Royal Marsden Hospital, London, UK presented intracranial efficacy findings on behalf of the ALTA-1L trial investigators. ALTA-1L compared the benefits of the next generation ALK inhibitor, brigatinib with the current standard, crizotinib in tyrosine kinase inhibitor (TKI) naive patients with stage IIIB/IV, ALK-positive non-small cell lung cancer (NSCLC). Patients were stratified by the presence of baseline brain metastases and prior chemotherapy regimens that had been received for advanced disease and randomised 1:1 to receive brigatinib at 180 mg daily with a 7-day lead-in at 90 mg or crizotinib at 250 mg twice daily. The primary endpoint of blinded independent review committee (BIRC)-assessed progression-free survival (PFS) had been met at first interim analysis and previously reported; median PFS was NR with brigatinib versus 9.8 months with crizotinib (hazard ratio [HR] 0.49; p = 0.0007). Secondary endpoints included intracranial objective response rate (iORR), and intracranial PFS (iPFS). An exploratory competing risks analysis of intracranial progression and systemic progression (both per systemic BIRC), and death was also performed.

Of the 137 patients receiving brigatinib and the 138 patents on crizotinib, 31% and 34% of patients had baseline brain metastasis (BIRC-assessed) and 13% versus 14% of patients had received prior brain radiotherapy, respectively. After a median follow-up in the respective cohorts of 11 and 9.3 months, iPFS in intention-to-treat (ITT) population was significantly improved with brigatinib compared to crizotinib (HR 0.42; 95% confidence interval [CI], 0.24-0.70; p = 0.0006).

Competing risks analysis of the ITT population found that the time to intracranial progression without prior systemic progression was also significantly improved with brigatinib versus crizotinib (HR 0.30; 95% CI, 0.15-0.60; p < 0.001) and the one-year cumulative incidence was 12% (95% CI, 6-20) versus 23% (95% CI, 15-31), respectively. The time to systemic progression without prior intracranial progression was improved with brigatinib compared to crizotinib (HR 0.51; 95% CI, 0.30-0.86; p = 0.017). The evaluation of intracranial efficacy results also showed that 16% of brigatinib treated patients versus 28% of crizotinib-treated patients had a PFS event; median iPFS was not reached (NR); 95% CI, NR) versus NR (95% CI 11-NR) months (HR 0.42; 95% CI, 0.24-0.70) and the one-year PFS rates were 78% versus 61%.

In the patients with baseline metastasis, 26% of the 43 patients on crizotinib had an iPFS event compared to 60% of 47 patients on crizotinib, median iPFS was NR (95% CI, 11-NR) versus 6 (95% CI, 4-9) months (HR 0.27; 95% CI, 0.13-0.54; p < 0.001) and one-year iPFS rates were 67% versus 21%, respectively. The iORR was 79% versus 23% (p < 0.0001) and the confirmed ORR was 67% versus 17% (p < 0.0001) with brigatinib versus crizotinib. In 18 versus 21 patients with measurable brain metastases in the respective treatment arms, the iORR was 83% versus 33% (p < 0.0023) and the confirmed ORR was 78% versus 29% (p < 0.0023) with brigatinib versus crizotinib. NCT02737501; Popat *et al.* Abstract LBA58

Practice point and future research opportunities

This analysis demonstrated that brigatinib has superior intracranial activity over crizotinib in ALK TKI naive patients with ALK-positive NSCLC. These findings confirm the earlier reported overall PFS findings. Brigatinib as a potential first-line option for patients with ALK-positive NSCLC is supported by this study and the trial reported in September 2018 in the *NEJM*.[1]

Citation:

1. Camidge DR, Kim HR, Ahn M-J, *et al.* Brigatinib versus Crizotinib in ALK-Positive Non–Small-Cell Lung Cancer. *New England Journal of Medicine* 2018; 379:2027-2039.

Patients with lung adenocarcinomas and specific uncommon EGFR mutations benefit more with chemotherapy than with TKI treatment

First author Aurelien Brindel of the Pathology Department, Groupement Hospitalier Est in Bron, France and colleagues conducted a retrospective study to determine the incidence of rare, uncommon epidermal growth factor receptor (EGFR) mutations and to describe the association of these mutations to patient response and outcome following chemotherapy or

tyrosine kinase inhibitor (TKI) therapy. TKIs targeting EGFR are a standard treatment in patients with lung adenocarcinomas. However, this analysis of a large database of sequenced EGFR results and corresponding patient outcomes has revealed uncommon EGFR mutations that indicate survival was improved following first-line chemotherapy compared with a TKI in these patients.

The investigators performed 7539 molecular analyses covering exons 18 to 21 of the EGFR from 2009 to 2017 at the regional genomics facility of the Lyon University Hospital using techniques such as Sanger and next generation sequencing. This analysis comprised EGFR-mutant tumours excluding L858R, exon 19 deletions, T790M, and exon 20 insertions. All mutations were reviewed by two pathologists, and clinical data were collected from the corresponding medical records of the patients.

Sequencing yielded 857 EGFR somatic mutations, of which 95 (11%) were considered to be uncommon EGFR mutations. The majority of uncommon mutations included 47 (50%) exon 18 mutations, comprised of 15% E709X and 35% G719X alterations. Twenty-six (27%) exon 20 mutations were found that included 9% of S768I and 18% of A767_V769dup mutations. In addition, 22 (23%) L861Q in exon 21 mutations were detected. Of further interest were 27 (28%) samples, which presented another mutation, of which 9 contained L858R mutations.

The corresponding patient data showed that patients with uncommon mutations had longer median overall survival (OS) when treated with first-line chemotherapy than patients with similar mutations receiving a first-line TKI; median OS was 27.7 months; (95% confidence interval [CI], 21.6-35) with chemotherapy compared to 16.9 months (95% CI, 13.6-25.9) with a TKI ($p = 0.075$, all mutations included). The investigators further correlated OS with the type of mutation and found that exon 18 and exon 20 mutations associated with a better prognosis, whereas L861Q was linked to a poorer prognosis. The presence of a second rare EGFR mutation in the same tumour sample associated with better OS ($p = 0.002$).

The investigators found that chemotherapy tended to improve survival compared to TKI therapy in patients with lung adenocarcinoma, who also presenting with uncommon EGFR mutations. Of note was that patients having specific mutations localised in exon 18 showed a better prognosis than others. Uncommon somatic mutations need to be further investigated in larger cohorts, as their clinical and therapeutic significance remains unknown. Brindel *et al.* Abstract LBA60

Practice point and future research opportunities

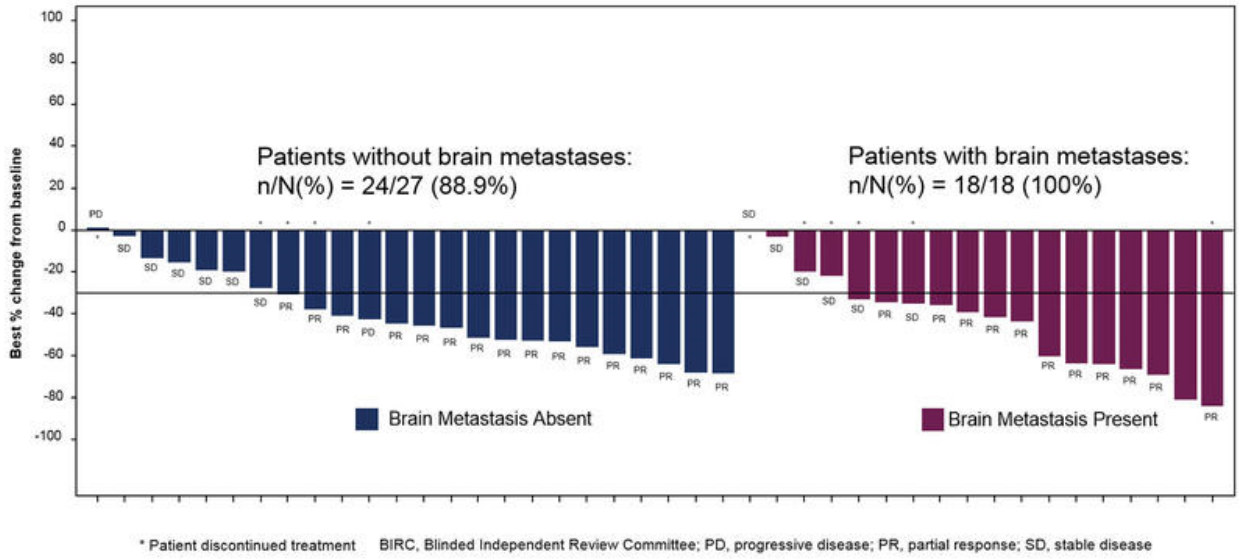
This study provides further insight on incidence of uncommon mutations in Caucasian patients. However, there are no data on overall response rate and progression-free survival, only one patient received osimertinib, and there are no data provided on clinical characteristics according to type of mutations.

First-line nazartinib shows promising anti-tumour activity in adult patients with EGFR mutated NSCLC

Daniel SW Tan, Medical Oncology, National Cancer Centre Singapore, Singapore presented primary efficacy and safety data from a trial of single agent nazartinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). He explained that nazartinib selectively targets L858R and ex19del activating mutations, as well as T790M resistance mutants, while sparing wild-type EGFR. Dr. Tan and colleagues conducted this phase I/II multicentre study of nazartinib in treatment-naive patients with advanced EGFR mutated non-small cell lung cancer (NSCLC) harbouring activating EGFR L858R and/or ex19del mutations. All 45 patients received the recommended phase II oral dose of 150 mg once daily on a continuous schedule. Their median age was 64 years, 60% of patients were female, and 62% were Asian. Fifty-eight percent had ECOG performance status 1 and 18 (45%) patients had brain metastasis at baseline. EGFR mutations were ex19del in 56% of patients, L858R in 40%, and 4% of patients had other EGFR mutations. Anti-tumour activity, including overall response rate (ORR) per RECIST v1.1, as assessed by blinded independent central review (BICR), served as the primary objective, and secondary objectives included safety, tolerability, and pharmacokinetics.

Nazartinib provided high ORR and disease control rate (DCR); 29 of 45 patients demonstrated a response to nazartinib, yielding an ORR of 64% (95% confidence interval [CI], 49%-78%). One patient achieved complete response. At data cutoff on 22 March 2018, responses were ongoing in 27 of the 29 responding patients. The 6-month duration of response rate (DoR) was 91%, and the median DoR was not estimable (NE). The DCR was 93%. The 6-month progression-free survival (PFS) rate was 83% (median NE) and the 6-month overall survival (OS) rate was 95% (median NE) with nazartinib. Evaluation of the 17 patients with baseline brain metastasis in non-target lesions showed 9 (53%) patients had resolution of brain metastasis. One of the 27 patients without baseline brain metastasis developed a new brain metastasis on study.

Figure: Waterfall plot of change from baseline in overall target lesions per BIRC in patients with or without brain metastases.



© Daniel SW Tan

The 45 patients in the entire population had a median exposure to nazartinib of 43.3 weeks. Frequently reported adverse events (AEs; any grade ≥ 20%) regardless of causality included diarrhoea (38%), maculopapular rash (31%), stomatitis (24%), cough (22%), decreased appetite (22%), pruritus (20%), and pyrexia (20%). The most frequently occurring grade 3 to 4 AE (in ≥ 5% of patients) was maculopapular rash, which was reported in 9% of the patients. Nazartinib therapy was discontinued by 9 patients due to progressive disease, one patient discontinued due to an adverse event, maculopapular rash, one due to patient choice, and one discontinuation was due to death. Tan *et al.* Abstract LBA61

Practice point and future research opportunities

These study findings point to nazartinib being an effective third generation EGFR-TKI with good brain penetration. The PFS, DoR and OS are not mature yet and there is a higher incidence of grade ≥3 rash than with osimertinib. However, it is questionable whether another third generation EGFR-TKI is currently needed.

Front-line alectinib provides superior outcomes compared with crizotinib in Asian patients with advanced ALK-positive NSCLC, with and without CNS metastases

Caicun Zhou, Medical Oncology, Shanghai Pulmonary Hospital in Shanghai, China and colleagues conducted the phase III open-label ALESIA trial of alectinib compared to crizotinib in Asian patients. Enrolled patients had ALK-positive stage IIIB/IV non-small cell

lung cancer (NSCLC) and ECOG performance status 0 to 2. Patients with asymptomatic CNS metastases were allowed. The patients were randomly assigned in a 2:1 ratio to receive alectinib at 600 mg daily (n=125) or crizotinib at 250 mg daily (n=62). Tumour and CNS imaging were performed at regular intervals. The primary endpoint was progression-free survival (PFS) by investigator according to RECIST v1.1, and secondary endpoints included PFS by an independent review committee (IRC), time to CNS progression, objective response rate (ORR), duration of response (DoR), overall survival (OS), CNS ORR, quality of life, and safety. The primary objective was to demonstrate that PFS in Asian patients was consistent with that reported in the global ALEX trial, wherein median PFS was 34.8 months with alectinib compared to 10.9 months with crizotinib (hazard ratio [HR] 0.43; 95% confidence interval [CI], 0.32-0.58).

After a median follow-up of 16.2 months for alectinib and 15.0 months for crizotinib, the risk of progression or death was significantly reduced with alectinib compared to crizotinib, according to investigator assessed median PFS of not estimable (NE) versus 11.1 months (HR 0.22; 95% CI, 0.13-0.38; p < 0.0001), respectively. The secondary endpoints were met and supported the primary endpoint. In addition, the PFS results were consisted with PFS results in the ALEX trial. Median PFS by IRC was NE with alectinib versus 10.7 months with crizotinib (HR 0.37; 95% CI, 0.22-0.61; p < 0.0001). In the respective treatment arms, investigator assessed ORR was 91.2% versus 77.4% (p = 0.0095), and median DoR was NE versus 9.3 months (HR 0.22; 95% CI, 0.12-0.40; p < 0.0001). Although OS data were immature, the event rates favoured alectinib; event rates were 6.4% with alectinib versus 21.0% with crizotinib. Median OS was NE in both groups (HR 0.28; 95% CI, 0.12-0.68; p = 0.0027).

Evaluation of the data from patients with measurable or non-measurable CNS baseline lesions revealed that alectinib demonstrated CNS activity; the CNS ORR (IRC) was 72.7% with alectinib versus 21.7% with crizotinib. Complete responses were achieved by 50.0% versus 13.0% of patients, respectively. The time to CNS progression according to IRC review favoured alectinib, cause-specific (HR 0.14; 95% CI, 0.06-0.30; p < 0.0001).

Although patients were on alectinib for a longer time they showed fewer grades 3 to 5 adverse events (AEs). Treatment duration was 14.7 versus 12.6 months with alectinib versus crizotinib, respectively. Grades 3 to 5 AEs occurred in 29% versus 48%, and serious AEs occurred in 15% versus 26% of patients on alectinib versus crizotinib, respectively. Seven percent of alectinib versus 10% of crizotinib patients discontinued treatment due to an AE. NCT02838420. Zhou *et al.* Abstract LBA10

Practice point and future research opportunities

The study findings pointed out that there are differences in study design in three studies ALEX, J-ALEX and ALESIA in terms of dose, population and stratification, but there are similar primary efficacy outcomes that confirm the significant improvement in PFS. While J-ALEX provided suggestive evidence, the ALEX and ALESIA confirmed the CNS efficacy of

alectinib. The ALESIA study confirmed the dose of 600 mg daily in an Asian population; however, there is no definitive evidence that 300 mg twice daily is associated with lesser outcomes. In terms of CNS efficacy, both ALESIA and ALEX confirmed the optimal CNS efficacy of alectinib at 600 mg bd.

Maintenance chemotherapy not recommended after carboplatin and weekly paclitaxel doublet chemotherapy in elderly patients with advanced NSCLC

Elisabeth Quoix, Pneumologie, Hopital Civil, Strasbourg, France noted that, although the benefit of maintenance chemotherapy with pemetrexed has been demonstrated in fit patients with metastatic lung adenocarcinoma and, to a lesser extent, in squamous cell carcinoma (SCC) administered with gemcitabine, these trials included just a few elderly patients, prompting Dr Quoix and colleagues to conduct the IFCT-1201 trial. This is the first study dedicated to elderly patients that evaluates switch maintenance chemotherapy.

This randomised phase III trial enrolled patients with non-irradiable stage III or stage IV non-small cell lung cancer (NSCLC) and no EGFR mutation or ALK rearrangement aged 70 to 89 years. The patients had not progressed following 4 cycles of induction therapy comprised of carboplatin plus weekly paclitaxel. This trial compared maintenance therapy with the follow-up of induction therapy. From May 2013 to October 2016, 632 patients were enrolled with a median age of 76.4 (range, 70 to 89) years, 76% of patients were male, and 85% of patients were performance status (PS) 0-1. Following induction therapy, 328 patients were randomised; 119 patients with non-SCC tumours received maintenance therapy with pemetrexed at 500 mg/m² on days 1, and 22 and 43 patients with SCC were treated with gemcitabine at 1150 mg/m² on days 1, 8, and 22. Second-line therapy with erlotinib was recommended in both arms. Enrolment requirements included PS 0-2, a Mini Mental Score >23, and Modification of Diet in Renal Disease creatinine clearance ≥ 45 mL/min. The primary endpoint was overall survival (OS).

The median number of maintenance cycles delivered was 4 (range, 1 to 38). Median OS in all patients from induction was 11.0 months (95% confidence interval [CI], 9.9-12). Median OS from randomisation was equivalent at 14.1 months (95% CI, 12-17) in the induction follow-up arm compared to 14 months (95% CI, 10.9-16.9) in the maintenance arm (hazard ratio [HR] 0.91; 95% CI, 0.71 - 1.16; p = 0.45). However, progression-free survival (PFS) was significantly longer in the maintenance arm; median PFS was 2.7 months (95% CI, 2.6-3.1) in the follow-up arm versus 5.7 months (95% CI, 4.8-7.1) with maintenance (HR 0.51; 95% CI, 0.4-0.64; p < 0.001). Second-line therapy was administered to 103 (63.6%) patients in the maintenance arm versus 133 (81.1%) patients in the follow-up arm. The safety profile was as expected. NCT01850303. Quoix *et al.* Abstract LBA56

Practice point and future research opportunities

This trial demonstrated that conducting drug trials in elderly patients is feasible. Although a PFS gain was demonstrated in this trial it did not translate to an OS benefit. Switch

maintenance chemotherapy should not be recommended in elderly patients with advanced NSCLC.

PALLIATIVE AND SUPPORTIVE CARE

Oncologist training has the greatest impact on preparing patients for shared decision making about palliative systemic treatment

Hanneke W.M. van Laarhoven, Medical Oncology, Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands, underscored the importance of effective shared decision making (SDM) regarding treatment options in advanced cancer. Professor van Laarhoven and colleagues investigated the separate and combined effects of oncologist training and a patient communication aid on SDM in consultations regarding palliative systemic treatment. They conducted this multicentre randomised, controlled 4-arm trial, which enrolled 31 medical oncologists and 194 of their patients with advanced cancer and a median life expectancy of <12 months. The oncologists were randomised to receive training or no training and patients were randomised to receive a patient communication aid or not. The oncologist training consisted of a reader, two group sessions, a booster feedback session, and a consultation room tool. The patient communication aid comprised a question prompt list and a value clarification exercise. An initial consultation for starting systemic treatment or an evaluative consultation regarding continuing or stopping treatment was audio-recorded for each patient. The primary outcome was observed SDM (OPTION12), rated by blinded assessors. Intervention effects were investigated with multilevel analysis; the analysis was planned at 80% power.

Audio-recorded consultations of 187 patients and 27 oncologists were available for analysis. The analysis found that oncologist training had a large effect on observed SDM among patients who did not receive a communication aid (d=1.4). The patient communication aid had no impact on SDM among untrained oncologists (d=0.03), and the effect of combined oncologist training and a patient communication aid was not cumulative and did not exceed the single effect of training ($M_{training\_aid}$=49.83; $M_{training\_no\ aid}$=49.49; $M_{no\ training\_aid}$=29.88; $M_{no\ training\_no\ aid}$=29.50). Netherlands Trial Registry 5489. Van Laarhoven *et al.* Abstract 1511O

Practice point and future research opportunities

In this study, oncologist training emerged as the most important factor in improved shared decision making regarding treatment and palliative care in advanced cancer, which was not augmented by providing the patients with a communication tool. Additional analysis may provide an understanding of the effects of both interventions on secondary outcomes, such as patient satisfaction and treatment decisions.

High potency multi-strain probiotic does not reduce the incidence of grades 3/4 chemotherapy induced diarrhoea but does lower the occurrence of any grade diarrhoea

Atul Sharma, Medical Oncology, B.R. Ambedkar Institute Rotary Cancer Hospital (AIMS), New Delhi, India, and colleagues evaluated the effect of a high-concentration multi-strain probiotic on chemotherapy induced diarrhoea (CID) and associated weight-loss, malnutrition, and treatment breaks. They reasoned that, since chemotherapy changes the composition of the native gut microflora, improving the balance of intestinal flora may reduce the incidence of severe grades of diarrhoea.

This randomised, double-blind, placebo-controlled single centre study enrolled 291 patients who were randomised to receive one sachet daily containing 900 billion colony forming units (CFU) of 4 strains of Lactobacillus, 3 strains of Bifidobacteria and 1 strain of Streptococcus thermophilus daily or a sachet of corn starch as placebo corn starting 14 days prior to chemotherapy initiation and continued for two weeks following completion of chemotherapy cycle 3. The primary endpoint was the incidence of grade 3 and grade 4 diarrhoea and an analysis of serum VEGF, clusterin, and faecal calprotectin was also planned. Enrolment took place from July 2010 to November 2014. Patient characteristics were similar between the randomised arms, including the type and site of cancer ($p = 0.882$), as well as chemotherapy regimen ($p = 0.492$), and the patients were similar in body weight at all study visits.

The analysis found that the probiotic regimen compared to placebo did not significantly reduce the incidence of grade 3 ($p = 0.088$) or grade 4 ($p = 0.050$) diarrhoea, and the use of rescue medication ($p = 0.44$). However, reduction was seen in the any grade diarrhoea, which occurred in 199 patients receiving probiotics versus 220 patients on placebo ($p = 0.019$). Additional significant reductions with probiotics versus placebo were seen in VEGF (829.5 ± 345.0 versus 1416.91 ± 379.9), calprotectin (485.1 ± 117.2 versus 617.40 ± 140.1), and clusterin (102.4 ± 38.0 versus 145.86 ± 31.5), respectively (all $p = 0.001$). The results indicate a limited role of the probiotic in reducing incidence of severe CID. However, it was able to significantly reduce all grades of diarrhoeal episodes, levels of VEGF, faecal calprotectin, and clusterin. Clinical Trial Registry India Identifier CTRI/2009/091/001042. Sharma *et al.* Abstract 1682O_PR

Practice point and future research opportunities

Due to the effect of the gut microbiome on response and toxicity in cancer patients treated with immune checkpoint inhibitors and the recently initiated trials with faecal transplantation to improve outcome of checkpoint inhibitors, this study is of interest. Currently unknown is whether probiotics used in this trial positively or negatively influenced the immune system. With more patients being treated with immunotherapy, before embarking on large-scale usage of probiotics to reduce chemotherapy induced diarrhoea, their effect on the immune system should be investigated. These data suggest that probiotics have the potential to be

a simple and novel approach in the reduction of chemotherapy induced diarrhoea; however, confirmatory studies are necessary. As probiotics are living microorganisms there is potential risk of iatrogenic infection in immuno-compromised cancer patients, therefore safety data and adverse events associated with probiotic administration could influence their future role in prevention of chemotherapy induced diarrhoea.

PSYCHO-ONCOLOGY

Post-traumatic growth and death anxiety in caregivers of cancer patients

Ali Alkan, Medical Oncology, Osmaniye Public Hospital, Osmaniye, Turkey, explained that post-traumatic growth (PTG) is a positive psychological change that occurs following a meaningful challenging or traumatic life event. Professor Alkan and colleagues conducted the multicentre Phoenix study to determine predictors of PTG and death anxiety in care givers of cancer patients and evaluate whether death anxiety showed a relationship to PTG. Caregivers of cancer patients were evaluated with structured questionnaires to assess the death anxiety, PTG and clinical parametres associated with them, using the validated PTG and the Templer death anxiety (TDA) scales.

The investigators surveyed 426 participants from August 2017 to April 2018 in 3 separate cancer centres; of these, 361 (84.7%) of respondents stated several factors that affected their daily life after the diagnosis. These factors included: being a spouse of the patient (p = 0.57), age more than 40 (p= 0.60), female sex (p = 0.055), being married (p= 0.11), having a sibling (p = 0.43), and high TDA scores (0 = 0.03) showed a relationship with high PTG scores. By multivariate analysis, high death anxiety (DAN) scores were the only parametre associated with high PTG scores. (odds ratio [OR] 1.6; 95% confidence interval [CI],1.02-2.5; (p =0.03). In multivariate analysis, female sex was the only risk factor associated with high death anxiety scores (OR 1.6; 95% CI, 1.1-2.8), although caring for elderly patients, female sex, having siblings, low income, not working, presence of chronic disease, and having a history of psychiatry admission were related to high death anxiety scores. There was a significant association between PTG and death anxiety scores (r=0.15; p = 0.001), and high death versus low anxiety scores, respectively, were associated with positive impacts on self-perception (37 versus 35; p = 0.02), philosophy of life (16.0 versus 13.0, p = 0.035), and changes in relationship (16.0 versus 14.0, p = 0.01). Alkan *et al.* Abstract 1539O

Practice point and future research opportunities

This study provides the first data regarding the association between death anxiety and post-traumatic growth and offers new insight into the impact of death anxiety on positive psychological changes in caregivers of cancer patients.

PUBLIC HEALTH POLICY

Magnitude of clinical benefit of cancer drugs and time to health technology assessment decisions in Europe

Thomas Hwang, Program on Regulation, Therapeutics, and Law, Harvard Medical School in Boston, USA, and colleagues investigated whether the time to heath technology assessment (HTA) decisions and drug reimbursement status, correlated with the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). The ESMO MCBS uses a rational, structured and consistent approach to grade the magnitude of clinical benefit that can be expected from anti-cancer treatments and a key goal is to highlight the cancer drugs having the greatest clinical benefit that should be rapidly made available by health authorities.

The investigators used ESMO-MCBS scores to determine the correlation with national benefit. They identified all new cancer drugs that had been approved by the European Medicines Agency (EMA) from January 2007 to December 2016 for the treatment of solid tumours, together with their indications for treatment. HTA scores regarding France and Germany and appraisal evidence plus reimbursement decisions for England, France, Germany, and Scotland were extracted as of January 2018. ESMO-MCBS v1.1 scores were calculated based on the trials submitted to HTA bodies for appraisal. “Highest benefit” was defined as scores of A or B in the neo/adjuvant setting and 4 or 5 in the palliative setting on the ESMO-MCBS scale, and scores of ‘moderate,’ ‘considerable,’ or ‘major’ benefit were defined according to the HTA authorities. Comparisons between drugs with the highest versus lower benefit were made using the Fisher’s exact test, Mann-Whitney test, Cohen’s kappa, and Cox proportional hazards models.

From 2007 to 2016, the EMA approved 47 drugs for 77 solid tumour indications. The median times from EMA approval to HTA decision were 188 days in France, 209 in Germany, 384 in Scotland, and 405 days in England. Drugs categorised as having the “highest benefit” according to ESMO-MCBS scores were associated with shorter times to a HTA decision in all countries except Scotland: France, median 154 compared to 198 days (hazard ratio [HR] 1.82; 95% confidence interval [CI], 1.06-3.13; p = 0.03); Germany, 203 versus 213 days (HR 2.24; 95% CI, 1.27-3.93; p = 0.005); and England, 302 versus 413 days; (HR 1.95; 95% CI, 1.10-3.46; p = 0.02); while in Scotland the median number of days for “highest benefit” drugs and HTA decision was 349 versus 402 days (HR 1.15; 95% CI, 0.65-2.03).

In France, 90% of the “highest benefit” drugs were reimbursed compared to 100%, in Germany, 92% in England, and 95% in Scotland. High concordance between ESMO-MCBS and HTA scores was found for categorisation of “highest benefit” in Germany and France only (κ 0.8), and (κ 0.6), respectively. Hwang *et al.* Abstract 1555O_PR

Practice point and future research opportunities

Without timely reimbursement decisions that are based on appropriate evaluation of a new medicine's benefits and cost-effectiveness, patients may miss out on potentially life-changing cancer medicines. Although the times varied among the countries evaluated, this statistical analysis found an association between anti-cancer drugs having the greatest clinical benefit and faster times to HTA decision in all countries evaluated excepting Scotland, and that nearly of these anti-cancer agents are approved for reimbursement in Europe. The ESMO-MCBS and ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) are grounding treatment choices in the best available evidence, helping to enhance decision making for both clinicians and healthcare providers, and making a major contribution to securing access to optimal cancer care for all patients, wherever they live.

Potential cost benefit with value-based prescribing of oral oncology drugs

Lead author Mark J. Ratain, Department of Medicine, The University of Chicago, Chicago, USA and Allen S. Lichter, Chair, Board of Directors, Value in Cancer Care Consortium in Ann Arbor, USA used a recent study of abiraterone as an example of an oral oncology agent that was administered in doses far in excess of what is needed to investigate whether the development of value-based dosing strategies incorporating lower doses, less frequent dosing, or even therapeutic substitution of various drugs could lower cancer treatment costs. The goal was to identify products that could bring about cost-savings in excess of 33%. Publicly available documents for all patent-protected oral oncology drugs that were approved in the US were reviewed, including official prescribing information, FDA Clinical Pharmacology reviews, and peer-reviewed publications that analysed the relationship of dose or drug exposure to efficacy. The investigators assessed the potential cost-savings using publicly available US pricing data, and also determined the potential impact on global sales. They identified drugs with flat pricing as those where dose reductions would not impact costs, and only considered opportunities to reduce dosing frequency for these agents.

However, they found that costs could potentially be reduced by 33% or more in 62% of the oral oncology products evaluated, and more than 50% reductions were possible for 49% of cancer agents. Using strategies such as dose reduction could lower the costs of 19 drugs; of these, 7 had positive food effect meaning that drug labels were labeled to be administered in fasted states, despite the fact that food increases their bioavailability.[1] Other strategies included frequency reduction in 13 drugs, and therapeutic substitution, such as sirolimus for everolimus. They determined the potential savings were 91.300 USD plus 33.000 USD (range, 35.700 USD to 186.400 USD) per patient-year for these 33 drugs according to current US flat pricing. Based on recent sales, the potential global savings opportunity was more than 12 billion USD per year, with approximately 75% of the potential savings encompassed by the top six treatments, including ibrutinib (2.6 billion USD), abiraterone (1.9 billion USD), enzalutamide (1.6 billion USD), everolimus (1.4 billion USD), nilotinib (0.9 billion USD), and erlotinib (0.7 billion USD). The authors underscored that this estimate is

likely conservative, given the expanding indications and prolonged treatment courses for many drugs, such as ibrutinib and abiraterone and pointed out that similar cost saving opportunities exist for parenteral monoclonal antibodies with long half-lives. Ratain *et al.* Abstract 1556O

Practice point and future research opportunities

Developing value-based prescribing strategies while maintaining the drug's efficacy has the potential to significantly impact prescribing costs of many oral oncology drugs.

Citation:

1. Kang SP and Ratain MJ. Inconsistent labeling of food effect for oral agents across therapeutic areas: differences between oncology and non-oncology products. Clin Cancer Res 2010; 16(17):4446–4451.

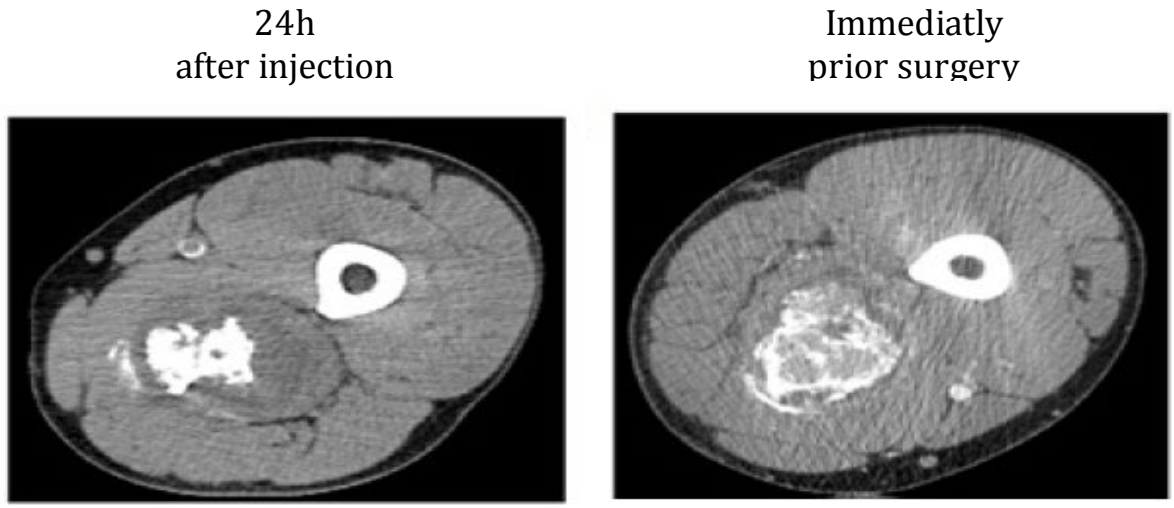
SARCOMA

Novel NBTXR3 provides a new option for preoperative treatment in patients with soft tissue sarcoma

Sylvie Bonvalot, Surgery, Institut Curie in Paris, France presented the results of an international, multicentre, randomised, open-label phase II/III trial of a novel agent, NBTXR3, which is a first-in-class Hafnium-Oxide nanoparticle. The trial enrolled patients with locally advanced soft tissue sarcoma (STS) of the extremity and trunk wall. Professor Bonvalot explained that this trial stemmed from a phase I study in STS, which showed that a single NBTXR3 intratumoural injection at 10% of the baseline tumour volume administered together with preoperative radiotherapy was technically feasible, and demonstrated both clinical activity and manageable toxicity.
The intent-to-treat (ITT) population in this trial comprised 179 patients who were randomised equally to be treated with a single intratumoural injection of NBTXR3 followed by radiotherapy or radiotherapy alone. Both treatment arms received subsequent surgical resection and the patients were stratified according to STS histological subtype. Radiotherapy comprised Intensity Modulated Radiotherapy or 3D-Radiotherapy of 2Gy/25 fractions to a total of 50 Gy. The primary endpoint was the pathological complete response (pCR) rate, which was defined as the percentage of patients presenting ≤5% of residual viable cancer cells (EORTC guidelines), as evaluated by a blind Central Review Board (BCRB). Key secondary endpoints included negative surgical margins (R0), and safety.

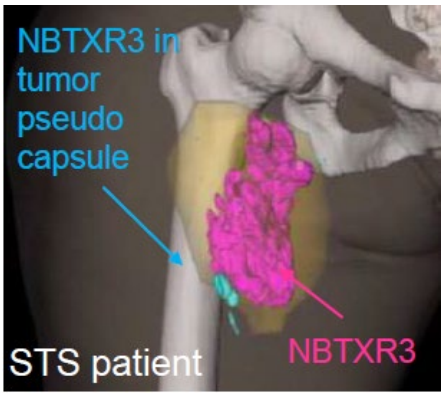
Twice as many patients who received NBTXR3 hafnium oxide nanoparticles activated by radiotherapy showed a pathological response than similar patients treated with radiotherapy alone; the pCR rate was 16.1% with NBTXR3/radiotherapy compared to 7.9% with radiotherapy ($p = 0.0448$). The R0 rate in the respective groups was 77.0% versus 64.0% ($p = 0.0424$).

Figure: CT-scan showing NBTXR3 (10%) intra-tumoural localisation.



From Bonvalot S *et al. Clin. Cancer Res.* 2017

Figure: 3D-reconstruction



© Sylvie Bonvalot

Twelve (13.5%) patients experienced injection-site pain and NBTXR3/radiotherapy was associated with grade 3/4 acute immune reactions in 7 (7.9%) patients. These adverse events were of short duration, manageable, and resolved spontaneously in some cases. Aside from the injection site reactions, NBTXR3/radiotherapy was very well tolerated and demonstrated a safety profile that was comparable to radiotherapy alone. NCT02379845. Bonvalot *et al.* Abstract LBA66

Practice point and future research opportunities

In this trial, NBTXR3 activated by radiotherapy was significantly superior to radiotherapy alone. The trial met both primary and secondary endpoints and a positive safety profile was demonstrated. NBTXR3 represents a new option for preoperative treatment in patients with locally advanced STS. NBTXR3 can be intratumourally injected and, following activation by radiotherapy, provides a higher energy deposit than radiotherapy alone and yields increased tumour cell death.

Findings from this trial support currently ongoing studies investigating NBTXR3 in recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) or metastatic non-small cell lung cancer (NCT03589339), HNSCC (NCT01946867; NCT02901483), prostate cancer (NCT02805894), liver cancer (NCT02721056]), and rectal cancer (NCT02465593).

SCLC

Atezolizumab versus chemotherapy as second-line therapy in patients with relapsed small-cell lung cancer

Jean Louis Pujol, Pneumologie, Hopital Arnaud de Villeneuve, Montpellier, France, and colleagues conducted the randomised, non-comparative phase II study IFCT-1603 trial to evaluate the activity of the PD-L1 antibody atezolizumab as systemic monotherapy in patients with small-cell lung cancer (SCLC) progressing after first-line platinum plus etoposide-based chemotherapy. Following 2:1 randomisation, 48 patients received atezolizumab at 1200 mg i.v. every three weeks until progression or unacceptable toxicity, and 26 patients received up to 6 cycles of investigators' choice of standard chemotherapy, such as second-line oral or i.v. topotecan or re-introduction of the carboplatin–etoposide doublet. Eligible patients were unselected for PD-L1 expression had ECOG performance status (PS) 0-2, and measurable disease by RECIST v1.1; however, patients on corticosteroid therapy, with a history of autoimmune disease, and patients with brain metastases were excluded. The primary endpoint was objective response rate (ORR) at 6 weeks with confirmation needed at 12 weeks. In the atezolizumab treatment arm, 83.7% of patients had PS 0-1, 79.6% had extensive disease, and 67.3% had shown progression within 90 days following the last dose of first-line chemotherapy.

Although the ORR and median progression-free survival (PFS) were better with chemotherapy, stable disease (SD) was more durable in patients responding to atezolizumab. At 6 weeks following atezolizumab treatment, one patient demonstrated response (ORR 2.3%; 95% confidence interval [CI], 0.0-6.8) and 8 (18.6%) patients had SD (95% CI, 7.0-30.2). Median PFS was 1.4 months (95% CI, 1.2-1.5) with atezolizumab. The ORR was 9.5% and 52.4% of patients achieved SD; median PFS was 4.2 months (95% CI, 1.5-5.9) with chemotherapy. At the time of reporting, 5 patients maintained SD in the atezolizumab group whereas no patients receiving chemotherapy maintained SD. Two (4.2%) patients experienced a grade 3 fatigue with atezolizumab and two patients developed grade 1 dysthyroidism. NCT03059667. Pujol *et al.* Abstract 1664O

Practice point and future research opportunities

In the IFCT-1603 trial, PD-L1 inhibition with atezolizumab did not increase the response or PFS over chemotherapy in relapsed SCLC. However, patients maintained stable disease for a longer time with atezolizumab than with chemotherapy.

TRANSLATIONAL RESEARCH

Liquid biopsy successfully monitors and predicts clinical benefit from chemotherapy and immunotherapy in advanced NSCLC

Laura Bonanno, Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy, presented findings on behalf of colleagues from a study that validated liquid biopsy as a tool for detecting tumour-specific genetic alterations in plasma samples from patients with EGFR-ALK-ROS1 wild-type (wt) advanced non-small cell lung cancer (NSCLC). The investigators also determined whether there was an association between the variation of mutations in plasma and outcome. They used plasma samples from patients being treated for advanced NSCLC in the prospective MAGIC-1 trial. The samples were obtained at baseline (T1), after the first treatment cycle (T2), at first radiological restaging (T3), and at radiological progression (PD; T4). Tumour DNA was screened through Mass Array (Sequenom) or next generation sequencing (NGS) and plasma DNA was analysed with Digital droplet PCR for *KRAS*-mutated patients and NGS for *KRAS*-wt patients. Semi-quantitative index of fractional abundancy (FA) of mutated allele was used.

The analysis presented at ESMO 2018 was from the 43 patients with mutated KRAS, including 11 patients treated with immunotherapy. At baseline, *KRAS* mutation in cell-free (cf)DNA was detected in 21 samples (49%; 95% confidence interval [CI], 33.3-64.5). The predictive value of *KRAS* mutation in plasma increased from T1 to T3. The predictive value of *KRAS* mutation was also statistically significant for PD, which was detected in 18 patients at T3, with an AUC 0.73 (95% CI, 0.55-0.91, p = 0.0132). Using a cut-off value of 0.013 FA, the sensitivity for PD was 58% (95% CI, 28-85) and the specificity was 89% (95% CI, 67-99). Any fractional abundancy reduction (T1-T3) showed an ability to discriminate between non-PD versus PD of 85% (95% CI, 72-97; p < 0.0001). The sensitivity for detection of non-PD was 67% (95% CI, 35-90) and the specificity was 89% (95% CI, 67-99).

Among patients treated with immunotherapy, the predictive value of fractional abundancy reduction (T1-T3) was 86% (95% CI, 58-100; p = 0.0124); the sensitivity was 100% (95% CI, 16-100) and the specificity was 86% (95% CI, 42-100). The only patient receiving immunotherapy died within 12 weeks and showed a fractional abundancy increase from 0 to 10% at T2. Plasma NGS analyses and an expansion cohort of patients treated with immunotherapy are ongoing. Bonanno *et al.* Abstract 1830O

Practice point and future research opportunities

This analysis showed that the dynamic variations of *KRAS* mutation in plasma significantly correlated with radiological disease control. Early variation of fractional abundancy of mutated alleles potentially identifies patients experiencing a poorer outcome with immunotherapy.

RELATED INFORMATION

Click here to access the Congress abstracts.

Click here to access the Congress webcast page.

Affiliations and Disclosure

Affiliation

Dr Svetlana Jezdic, ESMO Head Office.

Disclosure

No conflicts of interest to disclose.

Acknowledgement

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

ESMO would like to thank Drs George D. Demetri, Sheela Rao, Brian I. Rini, Toni K. Choueiri, Jonathan E. Rosenberg, Benoit You, Daniel SW Tan, and Sylvie Bonvalot for giving their permission to publish the images from the studies presented during the ESMO 2018 Congress in the ESMO Scientific report.

© Copyright 2018 European Society for Medical Oncology. All rights reserved worldwide.