European Lung Cancer Congress 2019 (ELCC)

10-13 April 2019

Geneva, Switzerland

Table of Contents

Summary

The 2019 edition of the European Lung Cancer Congress (ELCC) welcomed 1860 participants from around the world who gathered to discuss the latest developments in the quickly changing landscape of lung cancer research and clinical practice. Since its inaugural edition in 2008, the ELCC has secured its status as the premier annual meeting for professionals in the field. The abstracts chosen this year for presentation and discussion highlight cutting edge research and the most current treatment strategies in thoracic oncology that will influence patient care. A brief summary of a few of the diverse scientific findings presented at ELCC 2019 follows.

Introduction

The European Lung Cancer Congress (ELCC) 2019 was held from 10 to 13 April and was again set in Geneva, Switzerland. ELCC 2019 was organised by the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC) in partnership with the European Society for Radiotherapy and Oncology (ESTRO), and the European Thoracic Oncology Platform (ETOP). These leading oncology organisations represented an effort to advance science, promote education, and improve the practice of oncology worldwide. In collaboration, they hosted the premier lung cancer meeting in Europe, which drew 1'860 attendees, including 1'546 delegates, 117 faculty, 159 industry exhibitors, and 38 members of the press.

The delegates travelled from 75 countries located in Europe, Asia, North, Central, and South America, Africa, the Middle East, as well as Australia and the Pacific. This year, the largest proportion of delegates came for China (13.7%), followed by Switzerland (11.8%), and the United States of America (9.0%). Other highly represented countries included Germany (6.0%), Spain (5.3%), the United Kingdom (4.6%), Austria (3.5%), and France (3.1%). Of the delegates providing demographic information at registration, 46% were women and 54% were men. The average age of attendees was 44 years and majority (96.6%) was aged from 26 to 65 years.

The congress brought together practitioners of a broad range of healthcare professions, with clinicians (79.9%) comprising the largest group. Other groups represented were basic scientists (12.0%), pharmacists (4.0%), nurses (1.8%), patient advocates (0.9%), data specialists (0.9%), and undergraduate medical students (5%). The primary activity of delegates was medical oncology (48.91%), with a broad range of other activities from pneumonology to radiation oncology represented.

The primary interest in attending the congress expressed by participants was non-small cell lung cancer (56.8%). Nearly half (46.9%) of the delegates stated that they were interested in all chest malignancies, 38.9% stated an interest in small cell lung cancer, while 22.5% stated an interest in mesothelioma, and myriad other interests. Clinical research was cited by 46.7% of respondents as their primary area of interest, anti-cancer agents and cancer biology were each cited by 39.7%, and 38.1% of delegates said that leaning the most up-to-date advances in immunotherapy brought them to ELCC 2019.

ELCC 2019 received 311 scientific abstract submissions, which exceeded previous years. Of these, 210 were accepted and the remainder were rejected or withdrawn. The largest percent of submissions came from China (14.8%) and India (12.5%), with Italy, the United States, Germany, the United Kingdom, Spain, Portugal, and Switzerland contributing 8.4% to 2.9% of submissions. Together, France, Greece, the Netherlands, and the Republic of South Korea accounted for 1.9% of submissions. Of the accepted abstracts, 19% were presented in oral or mini-oral sessions, with the rest being presented as quality posters. Most (42.4%) of the accepted abstracts involved non-small cell lung cancer, with topics

including translational research, tumour biology, staging and screening, metastases to and from the lung, and other relevant topics also being covered.

ELCC provided a platform for the lively exchange of ideas across all thoracic tumour disciplines and interests. A brief summary of the advances that were presented at ELCC 2019 follows.

TUMOUR BIOLOGY AND PATHOLOGY

MET copy number is inversely proportional to PD-L1 expression in pleomorphic lung carcinoma tumour cells

Adam Januszewski from the Department of Thoracic Medicine, Royal Marsden Hospital NHS Foundation Trust in London, UK explained that pleomorphic lung carcinoma is a rare subtype of non-small cell lung cancer (NSCLC) that responds poorly to systemic therapy. Although pleomorphic lung carcinoma is a heterogeneous tumour having both epithelial and sarcomatoid components, targetable *MET* variants have been recently detected. To further characterise the molecular components of pleomorphic lung carcinoma, Januszewski and colleagues determined the PD-L1 expression levels in pleomorphic lung carcinoma and investigated the relationship of PD-L1-positive tumours and *MET* variants. The investigators searched the biobank and diagnostic archives of Royal Brompton Hospital and Imperial College Healthcare NHS Trust to identify 80 patients diagnosed with pleomorphic lung carcinoma that also had tissue samples. Of these, 78 cases were evaluated for PD-L1 status by immunohistochemistry, which was scored independently by two pathologists; >49% tumour expression was defined as high. DNA was also extracted and the *MET* copy number (CN) was determined by digital droplet PCR and genomic *MET* aberrations were detected by next generation sequencing.

The median PD-L1 score was under the cut-off value at 44%. Of 63 cases, 23 (36%) cases had a *MET* CN of >2.2. *MET*ex14 splice variants were identified in 5 of 73 (7.2%) cases and 2 of 73 (2.7%) cases had deleterious *MET* mutations. Evaluation of PD-L1-positive status by MET CN revealed median PD-L1 expression was higher (50%) in the 37.5% of cases that had low/normal (<2.3) *MET* CN than in the 37.5% of cases with high *MET* CN≥2.3 ($p = 0.18$); therefore, significantly fewer high PD-L1 expressers (>49%) were observed in cases with high *MET* CN>2.2 ($p = 0.06$). No significant difference in PD-L1 expression between mutated *MET* compared to wild-type was detected ($p = 0.9$). In 37 cases with PD-L1 expression <50%, 20 (50%) patients had low MET CN <2.3 and 17 (74%) had MET CN ≥2.3. Conversely, PD-L1 expression of 50% or greater was observed in 20 (50%) cases with MET CN <2.3 and just 6 (26%) of cases with MET CN ≥2.3. Januszewski *et al.* Abstract 1O

Practice point and future research opportunities

High levels of PD-L1 expression are generally observed in pleomorphic lung carcinoma, this study demonstrated that the level of PD-L1 expression is inversely proportional to *MET* copy number. This has implications in the use of checkpoint inhibitors in patients with *MET* copy number gain in NSCLC. Further evaluation is needed to better understand the response to checkpoint inhibitors in patients with pleomorphic lung cancer and MET copy number gain.

PD-1 to CD8 ratio in tumour microenvironment may be an indicator for outcome in surgically resected NSCLC

Giulia Mazzaschi, Medical Oncology Unit, University Hospital of Parma in Parma, Italy and colleagues investigated the tumour immune microenvironment with high-throughput extracted radiomic features to identify prognostic and predictive biomarkers for the response to immunotherapy in patients with non-small cell lung cancer (NSCLC). Sixty patients that had recently undergone surgical resection for NSCLC were evaluated. Tumour immune microenvironment was assessed by a quantitative evaluation of PD-L1 levels and an extensive morphometric analysis of tumour infiltrating lymphocytes (TILs). From each CT scan, in addition to semantic characteristics, 841 radiomic features were extracted through an open-source (3d Slicer) software. Radiomic variables were subjected to statistical analysis to test their correlation with tissue immune profiles and survival outcome.

The investigators detected a cluster of 3 patients that showed oppositely regulated radiomic features using an unsupervised hierarchical model. These 3 patients had significantly reduced overall survival of 13 months compared to 33 months in the other 57 patients ($p < 0.01$). Disease-free survival was also shorter at 11 versus 25 months, respectively. These 3 patients shared similar semantic imaging characteristics, such as no effect on parenchyma and subsolid texture, as well as a tumour immune microenvironment displaying PD-L1^{low} and TILs^{low} levels.

Radiomic variables from these patients were then compared to those extracted from patients that were matched for both tumour immune microenvironment PD-L1^{low} and TILs^{low} and qualitative CT parameters but having a favourable survival outcome. The investigators used signal-to-noise ratio and T-test; the most significant oppositely regulated wavelet features ($p < 0.0001$) in the two clusters were Large Dependence Emphasis, Busyness, Cluster-Tendency and Gray Level Variance, which revealed that the PD-1 to CD8 ratio was the only parametre differentially expressed in the two groups. Mazzaschi *et al.* Abstract 2O

Practice point and future research opportunities

Higher order radiomic features associated with a specific TILs phenotype that may describe a radiologic signature that could be prognostic in NSCLC.

TRANSLATIONAL RESEARCH

Findings from a large pooled analysis confirm circulating tumour cells as an independent prognostic factor for survival in advanced non-small cell lung cancer

Colin R. Lindsay of the Christie NHS Foundation Trust in Manchester, UK and fellow investigators conducted the EPAC-Lung study, which was a pooled analysis of individual patient data to determine the clinical validity of circulating tumour cell (CTC) quantification as a prognostic factor in patients with advanced non-small cell lung cancer (NSCLC). Their analysis included reported and unreported data from 7 European NSCLC CTC centres for patients with advanced NSCLC who participated in CellSearch CTC studies from January 2003 to March 2017. Cox regression models, stratified by centre, were used to establish the association between CTC count and survival, and likelihood ratio (LR) statistics and c-indices were used to explore the added value of CTCs to prognostic clinico-pathological models. The analysis included data from 550 eligible patients, including 209 patients whose prognostic information was previously unpublished.

The investigators found that CTC counts of ≥2 and ≥5 per 7.5 mL were associated with reduced progression-free survival (PFS); ≥2 CTCs (hazard ratio [HR] 1.72; $p < 0.001$); ≥5 CTCs (HR 2.21; $p < 0.001$). A relationship was also determined between CTC counts and overall survival (OS); ≥2 CTCs (HR 2.18, $p < 0.001$); ≥5 CTCs (HR 2.75; $p < 0.001$). Survival prediction was significantly improved by addition of baseline CTC count to LR clinico-pathological models; log-transformed CTCs ($p < 0.0001$); ≥2 CTCs ($p < 0.0001$); ≥5 CTCs ($p < 0.0001$).

There was minor evidence of between-centre heterogeneity in the effect of CTCs on PFS, but not OS. No difference in CTC profile was observed across key molecular subsets of NSCLC, including alterations of *EGFR, ALK*, or *KRAS.* Lindsay *et al.* Abstract 21O

Practice point and future research opportunities

This is the largest study of its kind in NSCLC. These findings confirm CTCs as an independent prognostic indicator of progression-free and overall survival in advanced NSCLC. The prognostic value of the CTC count was improved when added to full clinico-pathological predictive models. The investigators established ≥2 CTCs as an appropriate cut-off for clinical utility.

PREVENTION, EARLY DETECTION, EPIDEMIOLOGY, TOBACCO CONTROL

Findings from a French pilot study demonstrate the feasibility of lung cancer screening by low dose computed tomography scan

Olivier Leleu of the Centre Hospitalier d'Abbeville in Somme, France and colleagues conducted the DEP KP80 study to verify the results of 2 large randomised controlled trials, the NLST and NELSON, which found that annual low dose computed tomography (CT) screening among selected current or former smokers provided a significant decrease in lung cancer mortality. This single-arm, prospective study assessed the feasibility and effectiveness of a lung cancer screening pilot programme employing a low dose CT scan. DEP KP80 was initiated in May 2016 and ended in December 2018 in the French department of Somme. The study used the inclusion criteria in the NLST study and an annual low dose CT scan was scheduled with 2 additional screens planned. Nodules <5mm were considered negative, and nodules >10mm were positive; a 3-month CT with measurement of the doubling time was recommended for nodules from 5 to 10 mm. The protocol encouraged smoking cessation and the study was managed by the departmental cancer-screening agency (ADEMA80). All general practitioners, pulmonologists, and radiologists from the department were solicited by mail to participate in this study. Subjects were selected by the general practitioner or pulmonologist who checked the inclusion criteria and prescribed the CT scan.

In the first screening round, 218 general practitioners, 17 pulmonologists, and 28 radiologists participated. During a 2.5 year interval, 1307 subjects were recruited. The participation rate was 73%, with 949 scans being performed. Screening was negative in 733 (77%) cases, positive in 54 (5.7%), and indeterminate in 162 (17%) cases. The prevalence of a detected lung cancer was 2.5%. In all, 24 cancers were detected, comprising 16 adenocarcinomas, 3 squamous cell carcinomas, 1 carcinoid tumour, 2 small cell carcinomas, one undetermined, and one unknown. Of these detected cancers, 2 (8%) were carcinoma in situ, 13 (54%) were Stage IA, 3 (12%) were Stage IIB, 2 (8%) Stage IIIA, and 4 (17%) were Stage III B,C. Twenty (83%) of these patients underwent surgery and one patient had surgery for a benign lesion. Leleu *et al.* Abstract 43O

Practice point and future research opportunities

This study demonstrates the feasibility and effectiveness of an organised and structured lung cancer screening programme using low dose CT scan at the regional level.

IMAGING AND STAGING

Radiogenomic signatures in non-small cell lung cancer may provide a potential non-invasive imaging marker for *ALK* mutation

Shweta Wadhwa, Radiodiagnosis, Tata Memorial Centre in Mumbai, India discussed the utility of radiogenomic MRI signatures in the identification of anaplastic lymphoma kinase (ALK)-positive brain metastases in non–small cell lung cancer (NSCLC). Professor Wadhwa and colleagues undertook this study to analyse MRI data genomic parametres and correlate them with *ALK* mutation status. The investigators retrospectively reviewed data from 75 patients with NSCLC who were tested for *ALK* mutation and underwent multiparametric MRI imaging at diagnosis. Univariate logistic regression analysis was conducted to look for associations between *ALK* mutation status and various clinical factors, including sex, age, smoking, histology, TNM stage, and imaging characteristics.

Out of 75 patients, 46 were *ALK*-positive and 29 were ALK-negative. Analysis showed that *ALK*-positive mutations associated with a variety of lesion morphology characteristics, that often included a fuzzy and infiltrative T2w border with hypointense peripheral solid rim, compared with *ALK*- lesions, which frequently had a well-defined T2w border with no solid rim ($p < 0.001$).

On T1w, most *ALK*-positive lesions were heterogeneous, whereas *ALK*-negative lesions were predominantly hypointense ($p < 0.001$). Diffusion-weighted images showed that *ALK*-positive lesions exhibited central restriction ($p = 0.001$) and more often exhibited peripheral restriction of the solid rim than *ALK*-negative lesions ($p < 0.001$). *ALK*-positive lesions also had thick ring enhancement versus the patchy enhancement that was detected in *ALK*-negative lesions.

The incidence of meningeal involvement was significantly higher in *ALK*-positive cases and was absent in 80% of *ALK*-negative lesions ($p = 0.02$). MRI also revealed that just over half (54.3%) of *ALK*-positive patients had meningeal involvement, compared with just 17.2% of *ALK*-negative patients ($p = 0.02$).

On univariate logistic regression analysis *ALK*-positive mutation associated with younger age, smoking history, T2W lesion morphology, T2W border, restricted diffusion, enhancement, and meningeal positivity ($p < 0.05$). Wadhwa *et al.* Abstract 55O.

Practice point and future research opportunities

Patients with NSCLC lesions harbouring *ALK* rearrangement carry a higher risk of developing brain metastases. These findings show that *ALK*-positive brain metastases have specific MR imaging features that can be used as non-invasive diagnostic and predictive imaging biomarkers. MR radiogenomics have a potential role in individualised management of *ALK*-positive NSCLC brain metastasis.

SMALL CELL LUNG CANCER

Immunotherapy as maintenance treatment does not provide a survival advantage in extensive-stage small cell lung cancer

No overall survival (OS) advantage was obtained from maintenance therapy with nivolumab alone or in combination with ipilimumab over placebo in patients with extensive-stage small cell lung cancer (SCLC), according to findings presented by Taofeek Owonikoko, Co-Chair of the Clinical and Translational Review Committee, Winship Cancer Institute of Emory University in Atlanta, USA. Professor Owonikoko discussed results from the double blind, randomised, phase III CheckMate 451 trial, which enrolled 834 patients with extensive-stage SCLC and stable disease after 4 cycles of chemotherapy. The patients were randomly assigned 1:1:1 to receive nivolumab plus ipilimumab, nivolumab alone, or placebo for up to 2 years or until disease progression. In the combination arm, 279 patients received a maximum of 4 cycles of nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks, followed by nivolumab 240 mg every 2 weeks. Nivolumab monotherapy was administered at 240 mg every 2 weeks to 280 patients, and placebo was delivered to 275 patients. Patient baseline characteristics were well balanced across treatment arms; 23%, 22%, and 22% of patients in the combination, nivolumab, and placebo arms had received prior post-chemotherapy immunotherapy, and 63%, 66%, and 58% of patients in the respective arms had received first-line carboplatin-based chemotherapy.

The best response to chemotherapy was complete response in 3%, 2%, and 2%, and partial response in 72%, 69%, and 70% of patients in the combination, nivolumab, and placebo arms, respectively. In the respective groups, 25%, 29%, and 28% of patients showed stable disease following chemotherapy.

The primary endpoint, significantly improved OS with immunotherapy maintenance versus placebo, was not met. Subgroup analysis of OS revealed similar consistent results across subgroups of age, ECOG performance status, baseline LDH levels, the presence of liver metastasis at baseline, and the best response to prior chemotherapy. Only the subgroup of patients aged <65 years demonstrated OS that favoured the combination over placebo (median OS 10.2 versus 8.9 months, respectively, hazard ratio [HR] 0.72). In responding patients, the duration of response during maintenance therapy was 10 months with the combination, 11 months for nivolumab and 8 months for placebo.

However, patients beginning maintenance therapy ≤5 weeks post chemotherapy showed benefit from the treatment; median OS of 9.1 months (95% confidence interval [CI], 7.3-12.1) was observed with combination therapy and 12.1 months (95% CI, 9.6-12.1) with nivolumab versus 8.9 months (95% CI 7.3-11.0) with placebo (HR 0.83; 95% CI, 0.65-1.18 for combination versus placebo and HR 0.66 0.40-0.91; 95% CI, 0.49-0.91 for nivolumab versus placebo).

The rates of adverse events (AEs) were higher with combination immunotherapy; AEs

occurred in 86% of patients receiving the nivolumab/ipilimumab combination compared to 61% of patients treated with nivolumab, and 50% of patients on placebo. Fifty-four percent of patients receiving the combination discontinued the study due to a treatment related AE versus 12% of patients in the nivolumab arm and <1% of patients on placebo. Seven (2.5%) treatment-related deaths occurred with nivolumab plus ipilimumab, and one patient each died in the nivolumab and placebo groups. NCT02538666. Owonikoko *et al.* Abstract LBA1_PR

Practice point and future research opportunities

In SCLC approximately 60 to 70% of patients have extensive disease at the time of diagnosis and cannot be treated with radiotherapy. There is generally a good initial response to chemotherapy; however, the responses are often not durable and most patients experience disease progression within a short time, resulting in a high unmet need for new treatments in the second line and beyond for SCLC.

This negative trial may be signal the end of the story for maintenance immunotherapy in unselected SCLC patients, since a previous smaller study was also negative. Although the progression-free survival results seem positive, the design of the study means they cannot be considered because the primary endpoint was negative. In addition, there is concern about deaths and stopping treatment because of toxicity. Predictive biomarkers will be crucial for identifying patients with SCLC who could be treated with immune checkpoint inhibitors and should be assessed within prospective studies to better understand the complexity of the immune response.

EARLY STAGE NON-SMALL CELL LUNG CANCER

Feasibility of electromagnetic navigation bronchoscopy demonstrated in the prospective, multicentre NAVIGATE study

Kevin Lau, Cardiothoracic Surgery, St. Bartholomew's Hospital, London, UK discussed the NAVIGATE study, which evaluated the utility of electromagnetic navigation bronchoscopy (ENB), an image-guided approach that allows access to peripheral pulmonary lesions. NAVIGATE was a prospective global multicentre study of super Dimension™ ENB navigation system use in community and academic settings. Although some of the results from the study have been published[1], Professor Lau presented findings for the first time from a prespecified one-month interim analysis of safety and overall usage for the European cohort in NAVIGATE.

Of the 175 subjects enrolled at 8 European sites, 99.4% had complete one-month follow-up. ENB directed lung biopsy was performed in 174 (99.4%) patients and assisted in fiducial marking in 14 (8.0%) subjects. Lymph node sampling was attempted using EMB in 12 procedures, of which 9 used linear EBUS. General anaesthesia was used in 57%, radial EBUS in 4.0%, cone-beam CT in 9.7%, fluoroscopy in 41.7%, and rapid on-site evaluation in 17.9% cases.

EMB navigation was successful in 96.6% of biopsies. Lesions were located primarily (72.7%) in the peripheral third of the lung and in the upper lobe (62.6%); the median lesion size was 18.0 mm. A bronchus sign was present in 66.8% of cases. The median EMB planning time was 12.5 minutes and the median total procedure time (bronchoscope in to bronchoscope out) was 43.5 minutes, which included 32.9 minutes of EMB-specific navigation/sampling time (first entry to last exit of the locatable guide or extended working channel). The EMB-related pneumothorax rate was 7.4%, with 5.1% of subjects requiring intervention or hospitalisation. Adverse events (according to the EMB-related Common Terminology Criteria) grade ≥2 were bronchopulmonary haemorrhage in 2.3%, and grade ≥4 respiratory failures in 0.6% of patients. Longer follow-up is required to assess diagnostic yield. NCT02410837. Lau *et al.* Abstract 68O

Citation:

1. Khandhar SJ, et al. BMC Pulm Med 2017; 17:59.

Practice point and future research opportunities

The results from the European cohort of the NAVIGATE study suggest that EMB provides a safe platform to aid in lung lesion biopsy. This study demonstrated that multidimensional lung lesion biopsy, fiducial placement, and concurrent lymph node sampling can be carried out during a single anaesthetic event in either a community or academic setting.

Comprehensive profiling of genomic and T-cell receptor repertoire in localised lung adenocarcinomas from a prospective cohort study

Keneng Chen, Thoracic Surgery, Peking University People's Hospital, Beijing, China and colleagues focused on the characteristics and relationship of genomic and immune profiling in lung adenocarcinomas in a prospective study of 100 consecutive patients with pulmonary nodule who were scheduled for curative lung resection from June 2017 to July 2018. The investigators explored the T-cell receptor (TCR) repertoire in tissue and white blood cell (WBC) samples of the patients using next-generation deep sequencing of the complementarity determining region 3 (CDR3) of the TCR β chain. Target-capture deep sequencing of 1021 genes was used to detect genomic variations in paired tissue and plasma samples.

The most frequently detected mutations were *EGFR* (65.4%), *TP53* (36.5%), and *KRAS* (11.5%). *KRAS* was frequently (84.6%) enriched in mucinous adenocarcinoma. Samples of a high invasive subtype and samples with no ground-glass opacity status were likely to have increased tissue tumour mutational burden (TMB; $p = 0.0016$, and $p = 0.0012$, respectively), higher T-cell clonality ($p = 0.05$, and $p = 0.05$), and more HLA-los of heterogeneity events ($p = 0.038$, $p = 0.035$). The median tumour neoantigen burden (TNB) was 2 neoantigens per Mb, which showed a positive relation with TMB ($r=0.97$, $p < 0.0001$). *EGFR*-mutant co-occurring mutations were enriched in the *TGF*-beta, *PI3K-Akt*, hippo and leukocyte trans-endothelial migration pathway ($p < 0.05$). The investigators determined that patients with *EGFR* mutation showed lower TCR clonality and co-occurring decreased activity in the hippo or leukocyte trans-endothelial migration pathway. Alterations in DNA damage response pathways were identified in 15.8% patients, with these patients also having higher TCR clonality ($p = 0.03$).

A total of 35.3% of ctDNA-positive samples were found in Stage I lung adenocarcinomas (LUAD), with a mean ctDNA abundance of 0.18% (range, 0.012 to 3.3%). Analysis of TCR repertoire from available paired WBC samples showed no obvious characteristics. NCT03320044. Chen *et al.* Abstract 69O

Practice point and future research opportunities

This is the first prospective study to correlate genomic alteration and the T-cell receptor in localised surgical lung adenocarcinoma. Analysis of co-altered pathways of *EGFR*-mutant lung adenocarcinoma and the immune microenvironment may provide a better understanding for identifying biomarkers to aid in the choice of neoadjuvant therapy that may provide optimal benefit to patients.

Smoking status and prior history raise the risk of cardiac events following radical radiotherapy for lung cancer

Fei Sun, Oncology, The Leeds Teaching Hospital NHS Trust St. James University Hospital, Leeds, UK, and colleagues aimed to identify predisposing risk actors for cardiac events in patients after they receive radiotherapy for lung cancer. The investigators examined the electronic databases of two UK institutions to retrieve data for all patients who received radical radiotherapy (RRT) including stereotactic body radiotherapy (SBRT), radical fractionated radiotherapy, and chemoradiotherapy for lung cancer from January 2010 to December 2016, but excluding patients receiving multiple courses of chest radiotherapy. Charleston co-morbidity index and Qrisk 3 scores were calculated to determine the relationship of post radiotherapy cardiac events, including the time to such event, time to cardiac events to patient characteristics, such as pre-existing cardiac conditions, and patient cancer demographics. This ongoing analysis has enrolled 600 patients thus so far; of these, 29% of patients had pre-existing cardiac conditions.

At a median follow up of 31 months, 52 patients experienced cardiac events following radiotherapy. This cohort comprised 33 males with a median age of 73 years and a median Charleston score of 6. Four (12.5%) of these patients had received adjuvant radiotherapy and 10 (14.5%) patients had received concurrent chemoradiotherapy. No patients were never or ex-smokers, defined as <10 pack years; ex-smokers included 9 patients with <20 pack years, 15 with 20 to 40 pack-years, 9 with >40 pack-years. Nine patients were current smokers.

Of the cardiac events reported, 37% were ischaemic events, which were grade 5 in 19 patients and led to death in 7 patients. The majority (58%) of patients with an ischaemic event did not have a known pre-existing cardiac condition; of the 19 patients with an ischaemic event, 8 had a prior reported cardiac anomaly, including 4 patients with a previous myocardial infarction, 2 with ischaemic heart disease one patient each had arrhythmia and a valve abnormality.

Seventy-one percent of cardiac events post RRT occurred within the first two years. The highest incidence of cardiac events was observed in patients who underwent radical fractionated radiotherapy and concurrent chemoradiotherapy. A total of 8 pericardial effusion events were reported, 13 arrhythmic events, and 12 cardiac failure events. Nine of the 13 patients experiencing arrhythmic events had a history of previously reported cardiac events, including 2 patients with an myocardial infarction, 2 with ischaemic heart disease, and 2 patients with valvular abnormality. This work is ongoing to identify greater numbers of patients and to combine local data with data from national registry to aid analysis. Sun *et al.* Abstract 72O

Practice point and future research opportunities

This analysis detected a clinically significant proportion of patients who developed cardiac toxicity following radical radiotherapy for lung cancer. These cardiac events occurred much sooner after lung cancer radiotherapy than events reported with radiotherapy for breast cancer or lymphoma. Smoking plays a role, as a high proportion of patients experiencing a cardiac event were current or past heavy smokers.

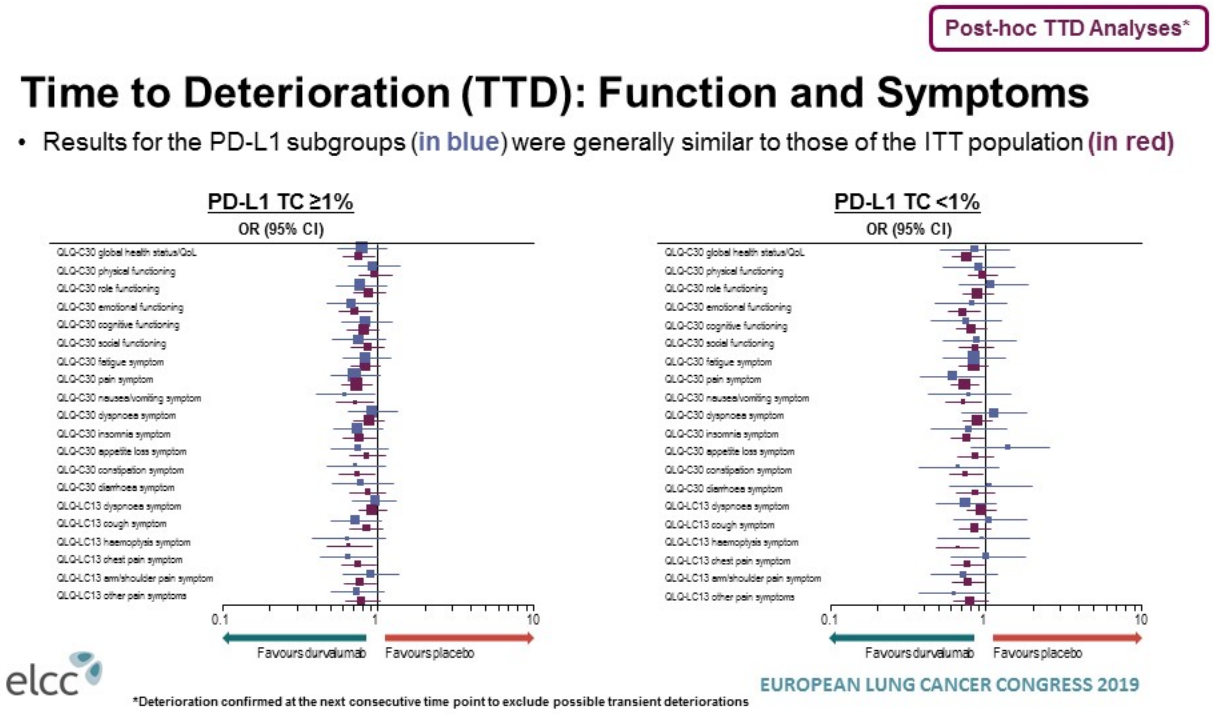
LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

Patient reported outcomes were consistent with the intention-to-treat population across PD-L1 subgroups in patients with stage III non-small cell lung cancer receiving durvalumab or placebo

Marina C. Garassino, of the Thoracic Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori in Milan, Italy and colleagues were prompted by results observed in the phase III PACIFIC trial to retrospectively investigate the impact of tumour PD-L1 expression on patient reported outcomes (PROs) to better understand the benefit/risk profile of durvalumab across all PD-L1 subgroups. In PACIFIC, durvalumab significantly improved the primary endpoints of progression-free and overall survival, and demonstrated similar safety versus placebo in patients with locally advanced non-small cell lung cancer (NSCLC), intention-to-treat (ITT) population. PROs revealed that no detrimental effect was reported with durvalumab or placebo across treatment groups. PACIFIC was conducted in patients with unresectable, stage III NSCLC who did not show disease progression following platinum-based concurrent chemoradiotherapy (cCRT); the patients received cCRT with ≥2 chemotherapy cycles; thereafter, patients were randomised 2:1 to durvalumab at 10 mg/kg or placebo i.v. every 2 weeks up to 12 months. If available, optional pre-cCRT tumour tissue was tested for PD-L1 tumour cell (TC) expression using the VENTANA SP263 immunohistochemistry assay and scored at pre-specified (25%) and post-hoc (1%) cut-offs. The patients were analysed according to PD-L1 expression: TC 25% status (<25%, ≥25%) and TC 1% status (<1%, ≥1%), and PD-L1 unknown. PROs were assessed using the EORTC Quality of Life Questionnaire 30 (QLQ-C30) and the lung cancer specific EORTC QLQ-LC13. The score range is 1 to 100 for both questionnaires, with higher scores on symptom scales representing greater symptom severity and higher scores on the global health status/QoL and functioning scales indicating better health status or function. Changes from baseline were derived and summarised overall and by PD-L1 status. Hazard ratios (HRs) for time to deterioration (TTD) were determined using a Cox proportional-hazards model, and odds ratios (ORs) for improvement rates were determined by logistic regression.

PD-L1 expression levels were generally not a factor in QoL. Of the 713 randomised patients, 63% provided a tissue sample of sufficient quality and quantity to determine PD-L1 expression and 37% patients had unknown PD-L1 status. The results of PRO analyses in the PD-L1 TC 25%, TC 1% and PD-L1 unknown subgroups for durvalumab compared to placebo were generally similar to those reported in the ITT population. Most PROs remained stable over time from baseline across all 5 PD-L1 subgroups, with no clinically meaningful differences observed between durvalumab and placebo, which was defined as a ≥10 point change from baseline. Results from pre-specified and post hoc TTD analyses of PROs by PD-L1 subgroup were also generally similar to those of the ITT population, with overlapping HRs and 95% confidence intervals. Similarly, improvement rates according to PD-L1 subgroups indicated PROs were generally similar to those of the ITT population, with overlapping ORs and 95% confidence intervals observed.

However, similar to the ITT population, clinically meaningful improvements from baseline at week 48 were observed across most PD-L1 subgroups for dysphagia (mean changes of -8.1 to -20.9) and for alopecia (mean changes -15.5 to -26.9) with durvalumab and for dysphagia (mean changes -10.4 to -19.4) and alopecia (mean changes -15.8 to -31.3) with placebo. Garassino *et al.* Abstract LBA2



Results for the PD-L1 subgroups were generally consistent with those of the ITT population, suggesting that patients' symptoms, functioning and global health status/QoL were maintained regardless of PD-L1 expression, including among patients with PD-L1 TC <1% (as shown here for the pre-specified time to deterioration analysis).

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Practice point and future research opportunities

This thorough analysis of PROs from the phase III PACIFIC trial that were evaluated according to the levels of PD-L1 expression demonstrated that QoL with durvalumab was similar to placebo in patients with advanced NSCLC across the ITT population and all PD-L1 subgroups, suggesting that QoL was not altered by PD-L1 expression.

Subsequent post-study immunotherapy impacts overall survival in patients with unresectable stage III NSCLC

Mario Ouwens, AstraZeneca in Gothenburg, Sweden and colleagues also used data from the phase III PACIFIC trial of durvalumab compared to placebo in stage III non-small cell lung cancer (NSCLC) to evaluate whether immunotherapy received after study discontinuation impacted the survival results. Both overall survival (OS) and progression-free survival endpoints were met in the study, which enrolled patients without disease progression following chemoradiotherapy for NSCLC. Post treatment discontinuation in PACIFIC, 41% of patients in the durvalumab arm and 54% of patients on placebo received additional treatment, including immunotherapy, which may have influenced OS. The investigators used the Rank Preserving Structural Failure Time (RPSFT) model, which is commonly used for analysis of trials allowing crossover, to quantify the specific impact of subsequent immunotherapy. They adapted the RPSFT model to isolate the likely effect of subsequent immunotherapy by assuming similar mortality risk reduction for nivolumab, pembrolizumab, and durvalumab. The RPSFT analyses utilised scenarios where no patients in either arm received subsequent immunotherapy, and a second scenario that compared the 54% of patients on placebo treated with immunotherapy as the first post study treatment to durvalumab patients who received no subsequent immunotherapy. The goal was to determine whether delaying immunotherapy was detrimental.

Subsequent immunotherapy was received by 8% of the patients randomised to durvalumab and by 22% of patients on placebo. The scenarios were compared to the overall intention-to-treat (ITT) population where the hazard ratio (HR) for OS with durvalumab versus placebo was 0.68 (95% confidence interval [CI], 0.53–0.87) and median OS was not reached (NR) versus 28.7 months, respectively. As may be expected, the patients receiving no subsequent treatment demonstrated minimal change in OS (HR 0.67; 95% CI, 0.52–0.86) and had median OS estimates that were similar to the ITT population. Data from the second scenario showed placebo patients receiving subsequent immunotherapy had a median OS of 32.2 months compared to NR in patients in the durvalumab arm receiving no subsequent immunotherapy (HR 0.79; 95% CI, 0.62–1.00). NCT02125461. Ouwens *et al.* Abstract 83O

Practice point and future research opportunities

After removing the effects of post study immunotherapy, the OS benefit with durvalumab was still evident compared with the ITT analysis.

The prevalence of tumour cell PD-L1 is stable among demographic, disease, and sample characteristics in unresectable, stage III NSCLC

David Planchard, Department of Medical Oncology, Institut Gustave Roussy in Villejuif, France presented findings on behalf of colleagues from an exploratory analysis of the prevalence of tumour programmed death ligand-1 (PD-L1) expression according to patient baseline disease and sample characteristics and by response to prior treatment. The

investigators used data from the phase III, randomised PACIFIC trial, which compared durvalumab with placebo in patients with unresectable, stage III non-small cell lung cancer (NSCLC) who did not show disease progression after concurrent chemoradiotherapy (cCRT). PACIFIC met both of the primary endpoints with patients on durvalumab showing significantly improved progression-free survival (PFS) and overall survival (OS), and also demonstrating similar safety as placebo.[1]

The investigators retrospectively tested archived pre-cCRT tumour tissue for PD-L1 expression on tumour cells (TC) using the VENTANA PD-L1 (SP263) immunohistochemistry assay. PD-L1 levels were scored at validated pre-specified (≥25%) and post-hoc (≥1%) cut-offs. Overall PD-L1 prevalence was summarised in both treatment arms by subgroups defined by various characteristics, and assessed using a Pearson's chi-squared test for between-group differences.

Of the patients participating in PACIFIC, 451 (63.2%) were evaluable for PD-L1 status. In these patients, 67.2% had tumour cell PD-L1 levels ≥1% and 35.3% had tumour cell PD-L1 expression ≥25%, which was similar to previous reports in metastatic NSCLC. No significant differences in tumour cell PD-L1 expression levels were observed according to race (White versus Black, Asian, or other) p = 0.5882, region (Asia versus Europe and North or South America) p = 0.2542, age (<65 versus ≥65 years) p = 0.7418, and sex p = 0.2973. Similarly, differences according to smoker versus non-smoker status (p = 0.5956), histology (squamous versus non-squamous; p = 0.2973), and ECOG/WHO performance status (p = 0.5236) also did not reach statistical significance. Differences in PD-L1 expression levels were statistically non-significant regarding disease stage (p = 0.5029), *EGFR* mutation status (p = 0.1176), best response to prior therapy (p = 0.1611), the location of the biopsy sample (p = 0.8045), specimen type (p = 0.4461), specimen age (p = 0.0902), and the collection method used (p = 0.5879). NCT02125461. Planchard *et al.* Abstract 85O

Citation:

1. Antonia SJ, et al. NEJM 2017; 377:1919-1929. Antonia SJ, et al. NEJM 2018; 379:2342-2350.

Practice point and future research opportunities

No statistically significant differences were observed in the prevalence of PD-L1 in tumour cell samples according to the relevant subgroups at the TC ≥1% or TC ≥25% cut-offs. PD-L1 status was unaffected by patients characteristics such as age, sex, or race and by sample type, age, or biopsy location. These results suggest that PD-L1 expression in pre-cCRT diagnostic biopsies is stable, thereby supporting the use of either primary tumour or lymph node biopsies for PD-L1 testing.

Prophylactic cranial irradiation may have increased benefit in younger patients with stage III NSCLC

Willem J.A. Witlox, Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre in Maastricht, Netherlands, discussed findings from a subgroup analysis of the efficacy of prophylactic cranial irradiation (PCI) based upon age, gender, performance status (PS), disease stage and tumour type, prior surgery, chemotherapy cycles, thoracic radiotherapy dose, and the total concurrent chemo-radiotherapy treatment time. Previously reported findings from the phase III NVALT-11/DLCRG-02 study demonstrated that PCI provided following chemo-radiotherapy provided a significant decrease in the cumulative incidence of symptomatic brain metastases compared to observation (7% versus 27%) in patients with stage III non-small cell lung cancer (NSCLC) at two years (hazard ratio [HR] 0.23). The analysis calculated the two-year cumulative incidence rates and performed competing risk regression, with death of any cause as competing risk, to examine the time to symptomatic brain metastasis. The median was used as a cut-off value for continuous variables. The effect of PCI was only examined in cases where a significant initial result was observed.

This subgroup analysis included 174 patients; no significant differences were seen in the effect of PCI according to sex, PS, histology, disease stage, prior versus no prior surgery, the number of chemotherapy cycles, radiotherapy dose, or total time of concurrent chemo-radiotherapy.

However, analysis according to age revealed the incidence of symptomatic brain metastasis was significantly lower in older (>61 years) compared to younger (≤61 years) patients, likely due to higher numbers of adenocarcinoma in the younger patients group; the incidence was 7% in the subgroup of patients older than 61 years compared to 26% in the subgroup of patients aged 61 and younger (HR 0.25). When these patients were stratified by age, the effect of PCI was significant in younger patients where PCI significantly reduced the incidence of symptomatic brain metastasis in younger compared to older patients; the incidence was 9% versus 42%, respectively (HR 0.18). PCI did not have a significant impact on patients according to gender (HR 1.31), or PS 1 or 2 (HR 0.86, 2.12, respectively). NCT01282437. Whitlox *et al.* Abstract 86O

Practice point and future research opportunities

The sample size of this study may be too small to detect statistically significant differences. Therefore, these results are hypothesis generating only and would require prospective evaluation.

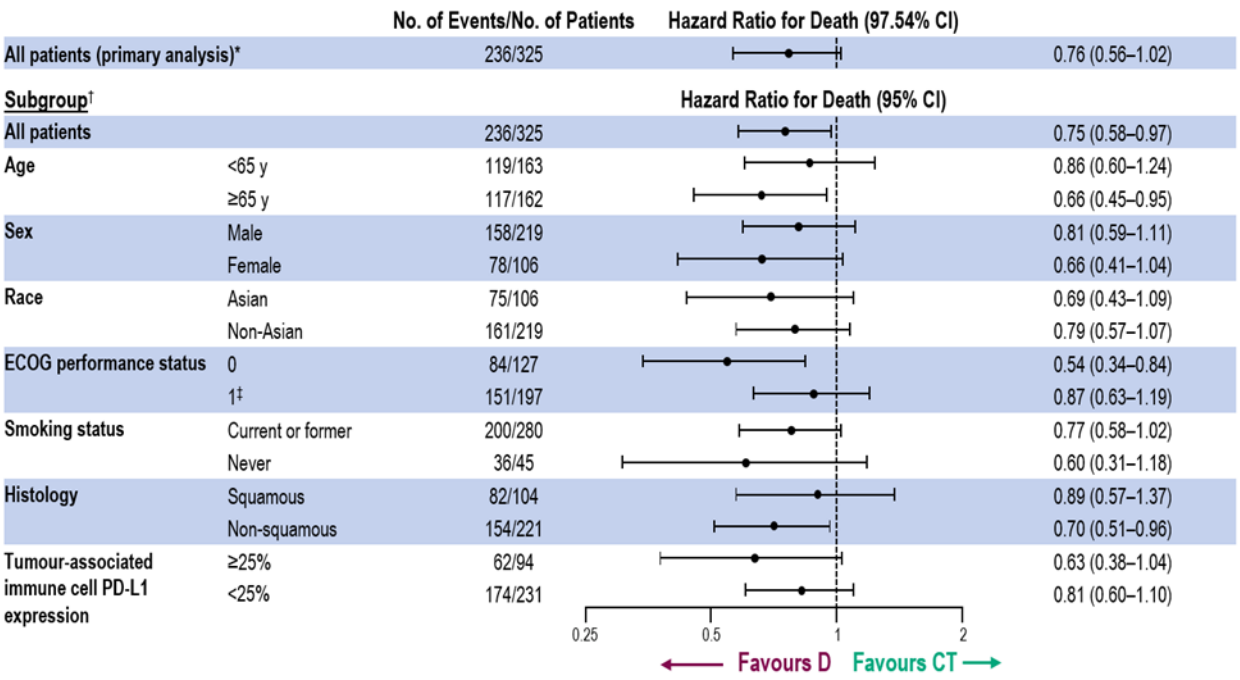
ADVANCED NON-SMALL CELL LUNG CANCER

Durvalumab benefit is consistent across a range of patient characteristics in first-line treatment for metastatic non-small cell lung cancer

Byoung Chul Cho of the Yonsei Cancer Centre, Yonsei University College of Medicine in Seoul, Republic of Korea discussed findings from a subgroup analysis of the MYSTIC trial. The analysis included 488 immunotherapy/chemotherapy-naïve patients with metastatic non-small cell lung cancer (NSCLC) who were randomised equally to receive durvalumab monotherapy at 20 mg/kg every 4 weeks, or durvalumab at 20 mg/kg every 4 weeks plus tremelimumab at 1 mg/kg every 4 weeks for 4 cycles (both durvalumab treatments were administered until disease progression), or up to 6 cycles of platinum-based chemotherapy. Baseline characteristics were well balanced between treatment arms. The investigators assessed overall survival (OS) with the three treatments according to prespecified baseline clinical characteristics that included age, gender, race, histology, smoking history, and tumour-associated immune cell (IC) PD-L1 expression (≥25% versus <25%). ECOG performance status (PS) was also included as a post-hoc variable.

Durvalumab monotherapy resulted in improvement in OS compared to chemotherapy across most clinical subgroups, including age ≥65 years (hazard ratio [HR]) 0.66; 95% confidence interval [CI], 0.45–0.95), non-squamous histology (HR 0.70; 95% CI, 0.51–0.96), PD-L1 IC ≥25% (HR 0.63; 95% CI, 0.38–1.04), and ECOG performance status 0 (HR, 0.54; 95% CI, 0.34–0.84).

Durvalumab plus tremelimumab provided similarly improved OS compared to chemotherapy in these subgroups: age ≥65 years (HR 0.72; 95% CI, 0.50–1.02), non-squamous histology (HR, 0.84; 95% CI, 0.61–1.14), PD-L1 IC ≥25% (HR 0.64; 95% CI, 0.39–1.05), and PS 0 (HR 0.76; 95% CI, 0.50–1.14).



*Primary analysis was based on stratified CPH model and had 97.54% CI; †Subgroup analyses were based on unstratified CPH model and had 95% CI; ‡Includes one patient with PS 2

Overall survival analyses across patient subgroups showed favourable HRs for durvalumab vs chemotherapy, consistent with the overall primary analysis in patients with PD-L1 TC ≥25%.

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The durvalumab plus tremelimumab arm showed the highest rates of treatment-related adverse events (TRAEs) leading to discontinuation, as well as immune-mediated AEs (imAEs). The rates of any TRAEs leading to discontinuation with durvalumab, durvalumab plus tremelimumab, and chemotherapy were 5.4%, 13.2%, and 9.4%, respectively, and the rates of any imAE in the respective groups were 13.6%, 28.3%, and 3.4%. The most commonly reported TRAEs leading to discontinuation in the respective cohorts were pneumonitis (0.8%, 1.9%, and 0.3%), and interstitial lung disease (0.5%, 1.3%, and 0.3%). The most frequently reported imAEs were hypothyroidism and pneumonitis, which occurred at rates of 5.7% and 2.2%, respectively, with durvalumab, 7.5% and 6.7% with durvalumab plus tremelimumab, and 0.6% and 1.4% with chemotherapy.

Patients treated with chemotherapy had the highest rates of grade ≥3 TRAEs; the rates for the occurrence of grade ≥3 TRAEs were 14.9% with durvalumab, 22.9% with durvalumab plus tremelimumab, and 33.8% with chemotherapy. The most commonly occurring grade ≥3 TRAEs in the chemotherapy arm were anaemia (10.2%) and neutropenia (9.9%). NCT02453282. Cho *et al.* Abstract LBA3.

Practice point and future research opportunities

This subgroup analysis of MYSTIC study data demonstrated that the OS analyses provided HRs favouring durvalumab compared to chemotherapy across most patient subgroups. These results were consistent with the overall primary analysis. The safety profile of durvalumab with or without tremelimumab was also consistent with previous studies; lower rates of grade ≥3 TRAEs were reported with durvalumab and the combination than with chemotherapy.

Exploratory analysis confirms improved survival with first-line durvalumab in metastatic non-small cell lung cancer after correcting for post study immunotherapy

Niels Reinmuth of the Asklepios Lung Clinic in Munich-Gauting, Germany presented results that demonstrated subsequent immunotherapy received primarily by patients in the chemotherapy arm of the phase III MYSTIC may have confounded the primary overall survival (OS) results and masked the true efficacy of durvalumab. Professor Reinmuth and a team of investigators used data from the phase III, randomised, open-label, MYSTIC study of first-line durvalumab with or without tremelimumab compared to chemotherapy in patients with metastatic non-small cell lung cancer (NSCLC). The trial enrolled immunotherapy/chemotherapy-naïve patients with metastatic NSCLC who were randomised equally to receive durvalumab monotherapy at 20 mg/kg every 4 weeks until disease progression, durvalumab at 20 mg/kg every 4 weeks until disease progression plus tremelimumab at 1 mg/kg every 4 weeks for 4 cycles, or up to 6 cycles of platinum-based chemotherapy. In-study crossover from chemotherapy to either of the durvalumab arms was not allowed, but subsequent post study treatment was recorded.

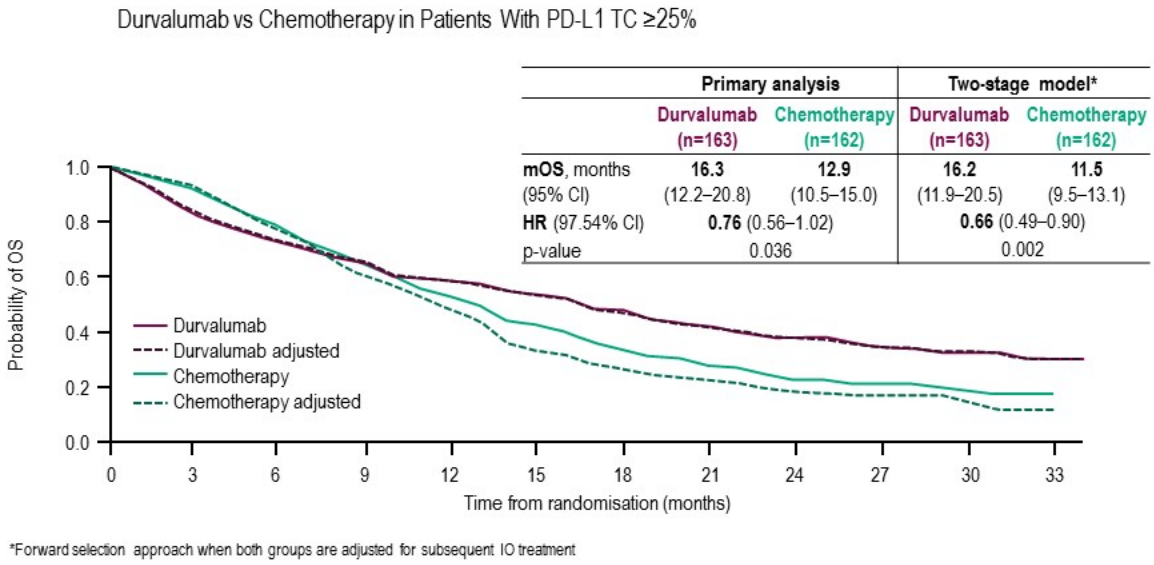
The previously reported primary analysis of MYSTIC data showed a clinically meaningful improvement in OS with first-line durvalumab versus chemotherapy in patients with metastatic NSCLC and tumour cell (TC) PD-L1 expression ≥25% (hazard ratio [HR], 0.76; 97.54% confidence interval [CI], 0.56–1.02; p = 0.036). However, the OS findings did not reach statistical significance, prompting this exploratory analysis.

As of 4 October 2018, 73 (44.8%) patients in the durvalumab arm compared to 95 (58.6%) patients in the chemotherapy arm had received subsequent treatment; 25 (15.3%) patients in the durvalumab arm and one (0.6%) patient in the chemotherapy arm remained on study treatment. In the group receiving subsequent treatment, 10 (13.7%) patients in the durvalumab arm and 64 (67.4%) patients in the chemotherapy arm were treated with additional immunotherapy, most commonly nivolumab and pembrolizumab, which were received by 1.8% and 2.5% of patients, respectively, of all patients originally randomised to durvalumab; 30.9% and 6.8% of all patients originally randomised to chemotherapy receiving nivolumab and pembrolizumab, respectively. Other immunotherapies included atezolizumab, durvalumab (chemotherapy arm only), or tremelimumab (chemotherapy arm

only). Cytotoxic chemotherapy was administered to 42.9% of patients in the durvalumab arm and 35.8% of patients in the chemotherapy arm.

The investigators used three statistical models to assess the effect of subsequent immunotherapy on OS in the durvalumab monotherapy and chemotherapy arms in the primary analysis population of patients with PD-L1 TC ≥25%: the rank preserving structural failure time (RPSFT) method, the inverse probability of censoring weighting (IPCW) method, and a two-stage method. They found that the two-stage method was the most appropriate for evaluating the effect of subsequent immunotherapy on OS. By this method, durvalumab significantly improved OS compared to chemotherapy (HR, 0.66 [97.54% CI, 0.49–0.90]; p = 0.002]). NCT02453282. Reinmuth *et al.* Abstract LBA4

Increased OS benefit with first-line durvalumab vs chemotherapy was observed after adjusting for the effect of subsequent IO using the two-stage model



*Forward selection approach when both groups are adjusted for subsequent IO treatment

Increased overall survival benefit with first-line durvalumab vs chemotherapy was observed after adjusting for the effect of subsequent immunotherapy using the two-stage model.

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Practice point and future research opportunities

This exploratory analysis investigated whether the primary OS analysis may have been affected by post-study immunotherapy. A markedly higher proportion of patients in the chemotherapy arm than in either durvalumab arm received subsequent immunotherapy, which may have confounded the primary OS outcome. This analysis demonstrated that OS

was improved with first-line durvalumab compared to chemotherapy after adjusting for the effect of subsequent immunotherapy.

First-line pembrolizumab continues to improve survival over chemotherapy in advanced non-small cell lung cancer with long-term follow-up

Tony Mok, Chinese University of Hong Kong, presented results from the final analysis of the phase III KEYNOTE-042 trial. KEYNOTE-042 randomly assigned 1274 patients with non-squamous non-small cell lung cancer (NSCLC) to receive either 35 cycles of pembrolizumab at 200 mg every 3 weeks or 6 weeks of standard paclitaxel/pemetrexed chemotherapy plus carboplatin with optional pemetrexed maintenance. Patients were stratified by region (east Asia/non-east Asia), ECOG performance status (0/1), histology (squamous versus non-squamous), and by PD-L1 tumour proportion score (TPS; ≥50% versus 1%–49%). The primary endpoint of overall survival (OS) had been met at the interim analysis of KEYNOTE 042 and previously reported. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety. Duration of response (DOR) was an exploratory endpoint.

Pembrolizumab demonstrated median OS of 16.7 months versus 12.1 months with standard chemotherapy in patients with advanced or metastatic disease and a TPS ≥1%, hazard ratio (HR) 0.81, p = 0.0018. At a median follow-up of 14 months, 6% of patients remained on pembrolizumab treatment and 3% were receiving pembrolizumab maintenance.

Treatment-related adverse events (TRAE) of grade ≥3 occurred in 113 (18%) patients in the pembrolizumab group and in 252 (41%) patients in the chemotherapy group. Thirteen (2%) on pembrolizumab and 14 (2%) patients on chemotherapy died due to a TRAE. NCT02220894. Mok *et al.* Abstract 102O

Practice point and future research opportunities

The OS benefit with pembrolizumab compared to chemotherapy was maintained with an additional 6 months of follow-up in patients with locally advanced/metastatic PD-L1–positive NSCLC without EGFR/ALK alterations. The FDA recently expanded the label for pembrolizumab monotherapy for the front-line treatment of patients with stage III NSCLC who are ineligible for surgery or definitive chemoradiation, as well as for patients with metastatic disease with a PD-L1 expression TPS level of 1% or greater who do not harbour *EGFR* or *ALK* aberrations.

Pembrolizumab efficacy and safety is similar in elderly and younger patients with PD-L1–positive advanced non-small cell lung cancer

Findings from an analysis of pooled data presented by Kaname Nosaki, from the National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan showed that pembrolizumab was safe and effective in elderly patients aged ≥75 years (range, 75 to 90 years). This

pooled analysis compared results from 264 elderly patients to those seen in 2292 participants younger than 75 years; all patients had PD-L1–positive advanced non-small cell lung cancer (NSCLC) and were participating in the KEYNOTE-010, KEYNOTE-042, and KEYNOTE-024 randomised trials, which compared pembrolizumab monotherapy and standard chemotherapy. In KEYNOTE-010, patients were randomised to receive pembrolizumab at 2 or 10 mg/kg every 3 weeks or docetaxel, as second- or later-line therapy. In the KEYNOTE-024 and -042 trials, patients, were randomised to first-line pembrolizumab at 200 mg every 3 weeks or platinum-based chemotherapy. Overall survival (OS) was the primary endpoint in all trials and was estimated by the Kaplan-Meier method.

All of the elderly patients had TPS ≥1% and 132 patients had TPS ≥50%. The OS favoured pembrolizumab over chemotherapy in the second-line and beyond setting across all TPS subgroups; in patients with TPS ≥1% (hazard ratio [HR] 0.76) and in patients with TPS ≥50% (HR 0.40). Patients with TPS ≥50% receiving pembrolizumab as first-line also showed improved OS; pembrolizumab versus chemotherapy (HR 0.41).

Fewer treatment-related adverse events (TRAEs) were reported in elderly patients treated with pembrolizumab than chemotherapy. Overall, in patients aged ≥75 years, 102 (68%) patients on pembrolizumab versus 99 (94%) of patients on chemotherapy had TRAE and TRAEs grade 3–5 occurred in 36 (24%) versus 64 (62%) patients in the respective treatment arms. Serious TRAEs were reported in 24 (16%) of pembrolizumab patients compared to 28 (27%) of chemotherapy patients and TRAEs leading to study discontinuation occurred in 16 (11%) versus 16 (15%) patients, respectively. TRAEs led to death in 2 (1%) patients receiving pembrolizumab and 2 (2%) patients on chemotherapy. On the other hand, immune-mediated AEs and infusion reactions were higher with pembrolizumab and occurred in 37 (25%) patients versus 7 (7%) elderly patients receiving chemotherapy, which was similar to younger patients treated with pembrolizumab (25%). KEYNOTE-010 (NCT01905657), KEYNOTE-024 (NCT02142738), and KEYNOTE-042 (NCT02220894). Nosaki *et al.* Abstract 103O_PR

Practice point and future research opportunities

It is important to investigate safety and efficacy in elderly patients since approximately 70% of newly-diagnosed NSCLC cases occur in the elderly, and more than half of these cases are locally advanced and/or metastatic. This pooled analysis of clinical trials showed no difference in the efficacy and safety of immunotherapy in the elderly compared to younger patients. Larger, prospective trials are needed to gain a more detailed view on the efficacy and safety of immunotherapy in elderly patients with NSCLC.

Real-life data suggest immunotherapy benefit may be decreased in elderly patients with advanced non-small cell lung cancer

In contrast to clinical trial data, overall survival (OS) results from a real-life study suggest that elderly patients may derive decreased benefit from immunotherapy. Elena Corral de la Fuente, Hospital Universitario Ramon y Cajal in Madrid, Spain discussed findings from a retrospective study of patients with advanced non-small cell lung cancer (NSCLC) who received immunotherapy in real-life clinical practice. These data suggested that elderly patients aged 70 or more years may have shorter overall survival than similarly treated younger patients. Professor Corral de la Fuente and colleagues reviewed data from all patients with advanced NSCLC treated with immunotherapy agents at their institution from 2014 to 2018. They identified 27 (27.5%) patients who were treated in first-, second-, and subsequent-line settings with immunotherapy and were aged 70 years or older. The patients' mean age was 62 years (range, 41 to 85), 73.5% were men, and 73.5% were smokers with more than 30 pack-years. In the study population 64.3% of patients had adenocarcinoma, squamous cell carcinoma was diagnosed in 25.5% of patients, and 41% of patients had mutated KRAS. The PD-L1 status was known in 50% of patients; 11% had PD-L1 expression <1%, 13% had levels from 1 to 49%, and 25% of patients had PD-L1 expression >50%. The majority (61%) of patients received immunotherapy in the second-line (61%) and 24.5% received immunotherapy in the third- or later line setting. Nivolumab was the most used drug in 52% of patients. In the overall cohort, the response rate was 32.7%, which included complete response in 5% and partial response in 28% of patients. The disease control rate was 55%.

A comparison of overall survival (OS) in elderly patients aged 70 and more years with patients younger than 70 years showed that OS was significantly shorter in the elderly patients; median OS was 5.5 months compared to 13 months, respectively, (hazard ratio [HR] 3.86; $p < 0.0001$). Progression-free survival (PFS) was also shorter in elderly versus younger patients; median PFS was 1.8 versus 3.6 months, respectively (HR 2.1; $p = 0.012$).

The safety analysis demonstrated no statistically significant differences in immune-related adverse events (irAEs) between elderly and younger patients ($p = 0.535$). The development of irAEs was associated with better PFS in younger patients (HR 0.45; $p = 0.012$) but did not significantly affect OS. Corral de la Fuente *et al.* Abstract 169P_PR

Practice point and future research opportunities

Although elderly patients aged ≥70 years represent the majority in advanced NSCLC, data are sparse regarding efficacy and toxicity for this age group, which is often under-represented in clinical trials. It may be that the age-related decline in the immune system affects immunotherapy efficacy. These results suggest that elderly patients could have worse survival outcomes with immunotherapy than younger patients, without differences in toxicity. This observational retrospective analysis had a small sample size. Nevertheless, this real-world study is an alarm that suggests potentially lower efficacy with immunotherapy in elderly patients despite no difference in adverse events. PD-L1 expression was known in only 50% of patients. Data collected in real-world studies are not controlled as precisely as in randomised trials, Larger, prospective trials or larger real-world studies are needed to

gain a more detailed view on the efficacy and safety of immunotherapy in elderly patients with NSCLC.

Immunotherapy-based combination regimen offers a new treatment option in patients with metastatic non-squamous non-small cell lung cancer and EGFR mutations

Martin Reck, Department of Thoracic Oncology at the Lung Clinic Grosshansdorf in Grosshansdorf, Germany presented findings from an exploratory analysis of the IMpower150 study, which included patients with epidermal growth factor receptor (EGFR) mutation, EGFR sensitising mutations, and patients with EGFR-mutated tumours that had received prior tyrosine kinase inhibitor (TKI) therapy. IMpower150 enrolled 1202 patients who were randomised equally to receive atezolizumab at 1200 mg plus carboplatin AUC 6 plus paclitaxel at 200 mg/m2 (arm A) or to atezolizumab plus bevacizumab at 15 mg/kg plus chemotherapy (arm B), or to bevacizumab plus chemotherapy (arm C). The agents were administered by i.v. every 3 weeks for 4 or 6 cycles per investigator decision, followed by maintenance with atezolizumab plus bevacizumab or single agent atezolizumab or bevacizumab, respectively. The primary endpoints were overall survival (OS) and investigatory-assessed progression-free survival in the intent to treat–wild-type population.

Professor Reck explained that the trial explored these combinations because atezolizumab inhibits PD-L1 to restore anticancer immunity and may be enhanced through the inhibition of VEGF immunosuppression by bevacizumab, which also promotes T-cell tumour infiltration, while chemotherapy with carboplatin plus paclitaxel may induce immune responses. The exploratory analysis representing ≥20-months of follow-up that included 79 (100%) patients with EGFR mutation; of these, 58 (73%) patients had EGFR sensitising mutations and 50 (63%) had received prior TKI therapy.

The IMpower150 trial demonstrated that atezolizumab plus bevacizumab and chemotherapy improved OS compared to bevacizumab plus chemotherapy in patients with EGFR mutation; median OS was not estimated (NE) versus 18.7 months, respectively (hazard ratio [HR] 0.61).

For the comparison of OS with atezolizumab/bevacizumab plus chemotherapy versus bevacizumab plus chemotherapy, all HRs favoured the quadruplet across the 3 subgroups; in patients with EGFR mutation median OS was NE in arm A versus 18.7 months in arm C (HR 0.61), in patients with EGFR sensitising mutations median OS was NE versus 17.5 months, respectively (HR 0.31), and in patients receiving prior TKIs median OS was NE versus 17.5 months (HR 0.39). The objective response rates in patients with EGFR mutation were 36%, 71%, and 42% and the median duration of response was 5.6 months (range, 2.6 to 15.2), 11.1 months (range, 2.8 to 18.0), and 4.7 months (2.6 to 13.5) in arms A, B, and C, respectively.

Serious adverse events (AEs) and immunological AEs were similar between the treatment arms. In patients with EGFR mutation, the safety analysis comprised 44 patients in arm A, 33 in arm B, and 44 patients in arm C. Treatment related AEs (TRAEs) occurred in 89%, 100%, and 96% of patients in arms A, B, and C, respectively; TRAEs grade ≥3 were reported in 57%, 64%, and 21% of patients in the respective groups. One grade 5 TRAE occurred in one (2%) arm C patient. Immune related AEs included rash in 36%, 30%, and 11% of patients and hypothyroidism in 2%, 18%, and 2% of patients in arms A, B, and C respectively. The IMpower150 trial results have been recently published in *Lancet Respiratory Medicine*.[1] Reck *et al.* Abstract 114O

Citation:

1. Reck M, *et al. Lancet Respir Med* 2019; 7(5):387-401.

Practice point and future research opportunities

Adding atezolizumab to bevacizumab and standard chemotherapy with carboplatin and paclitaxel improved OS in patients with metastatic non-squamous NSCLC and EGFR mutations who had failed prior treatment with TKIs.

IMpower150 is the first phase III immunotherapy-based combination study to demonstrate a statistically significant and clinically meaningful improvement in OS in patients with metastatic non-squamous NSCLC and EGFR mutation, providing a potential new standard of care for these patients.

Brigatinib versus crizotinib in advanced ALK-positive non-small cell lung cancer

Raffaele Califano, Consultant in Medical Oncology, NHS Christie Foundation Trust, in Manchester, UK reported results on behalf of colleagues from the first interim analysis of the ALTA-1L trial. The open-label, multicentre ALTA-1L study enrolled 275 patients with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who had received one or no prior systemic therapy for advanced NSCLC, including patients with symptomatic central nervous system (CNS) metastases. The patients' median age was 58 and 60 years, 26% and 27% of patients had received prior chemotherapy for advanced disease, and 29% and 30% of patients had brain metastases at baseline in the brigatinib and crizotinib cohorts, respectively. The patients were randomly assigned 1:1 to brigatinib at 180 mg once daily preceded by a 7-day lead-in (n=137) at 90 mg or to crizotinib at 250 mg twice daily (n=138). The primary endpoint was blinded independent review committee (BIRC)-assessed progression-free survival (PFS) by RECIST v1.1, and secondary endpoints included BIRC-assessed objective response rate (ORR), intracranial ORR (iORR), and intracranial PFS (iPFS).

At a median follow-up of 11.0 months with brigatinib and 9.3 months with crizotinib 99 PFS events had occurred. Brigatinib met the primary endpoint for statistical superiority over crizotinib, BIRC-PFS hazard ratio [HR] 0.49; log-rank p = 0.0007. Investigator-assessed median PFS was not reached (NR) with brigatinib versus 9.8 months with crizotinib, (HR 0.45; log-rank p = 0.0001). One-year PFS rates were 67% with brigatinib versus 43% with crizotinib and the systemic ORR were 71% versus 60%, respectively. The ORR with brigatinib comprised 4 confirmed complete responses (CR) and 67 partial responses (PR). With crizotinib there were 5 CR and 55 PR.

Regarding intracranial efficacy, 18 patients with baseline brain metastasis were assigned to brigatinib and 21 patients to crizotinib. These cohorts demonstrated iORRs of 76% versus 21%, respectively. With brigatinib, 11% of patients showed CR and 29% had PR, whereas with crizotinib the entire ORR consisted of 29% PR. The iORRs with more than one assessment were 83% versus 33% with brigatinib and crizotinib, respectively.

The most commonly reported treatment-emergent adverse events (AEs) grade ≥3 were increased blood creatinine phosphokinase (16.2%) and lipase (13.2%), and hypertension (9.6%) compared to increased alanine aminotransferase (9.5%), aspartate aminotransferase (5.8%), and lipase (5.1%) with brigatinib and crizotinib respectively. Any grade interstitial lung disease/pneumonitis occurred in 3.7% and 2.2%, respectively. Study discontinuations due to an AE occurred in 11.8% and 8.8% patients receiving brigatinib and crizotinib, respectively. NCT02737501. Califano *et al.* Abstract 106O

Practice point and future research opportunities

In this head to head comparison of brigatinib versus the current standard, crizotinib, brigatinib showed superior PFS and intracranial activity in patients with NSCLC who were ALK mutation-positive and naive to ALK inhibitor treatment.

Brigatinib demonstrated statistically and clinically superior PFS in the intention-to-treat population; in addition, in the cohort of patients with brain metastasis at baseline, brigatinib significantly delayed intracranial progression compared with crizotinib.

Longer follow-up supports continued crizotinib treatment in advanced ROS1-rearranged non-small-cell lung cancer

Session chair Tony Mok presented findings from the ongoing phase I PROFILE 1001 study on behalf of lead author Alice Shaw, Massachusetts General Hospital Cancer Centre in Boston, USA, whose flight was delayed. Previously reported efficacy data[1] showed that crizotinib was well-tolerated and provided a meaningful clinical benefit for patients with advanced ROS1-rearranged non-small cell lung cancer (NSCLC); the objective response rate was 72% and the response was durable with a median duration of response of 18 months.

At ELCC, updated overall survival (OS) and safety findings were presented after an additional follow-up of more than 3 years. The patients had histologically confirmed NSCLC containing ROS1 rearrangements that were detected by fluorescence in situ hybridization or reverse transcriptase polymerase chain reaction. All 53 patients received oral crizotinib at 250 mg twice daily from October 2010 to June 2018; the median duration of treatment was 22 months (95% confidence interval [CI], 15-36 months.

At data cut-off on 30 June 2018, the median treatment duration was approximately 8 months longer than that used in the primary endpoint analysis and 12 (22.6%) patients remained on treatment; 30.2% of patients were on crizotinib for more than 4 years. Median OS was 51 months (95% CI, not reached) and the probabilities of survival at 12, 24, and 48 months were 78.8%, 67.0%, and 50.7%, respectively.

No new safety signals were noted; at a median follow-up of 63 months, 26 (49.1%) deaths had occurred. The most common grade 3 treatment-related adverse events (TRAEs) occurring in ≥5% of patients included hypophosphatemia in 15.1%, and neutropenia in 9.4% of patients. No grade 4 TRAEs, treatment-related deaths, and no permanent discontinuations associated with TRAEs were reported. NCT00585195. Shaw *et al.* Abstract 107O

Citation:

1. Shaw AT, *et al. NEJM* 2014; 371:1963-1971.

Practice point and future research opportunities

The OS analysis with additional follow-up and updated safety information from the ongoing PROFILE 1001 trial continue to support the favourable benefit/risk profile of crizotinib for the treatment of patients with advanced ROS1-positive NSCLC.

High response rates demonstrated with entrectinib in ROS1-positive non-small cell lung cancer

Fabrice Barlesi of Marseille University, Assistance Publique-Hopital du Marseille in Marseille, France presented results from an integrated efficacy analysis of two phase I entrectinib studies, ALKA-372-001, STARTRK-1, and the phase II STARTRK-2 trial. The studies enrolled patients with non-small cell lung cancer (NSCLC) who had not received prior treatment with a ROS1 inhibitor but harboured a ROS1 fusion, as determined by nucleic acid-based diagnostic platforms. Tumour assessments were done at week 4 and every 8 weeks thereafter by blinded independent central review (BICR) by RECIST v1.1.

The efficacy population comprised 53 patients with a median age of 53 years (range, 27 to 73). Sixty-four percent of patients were female, approximately half (50.9%) of the patients were ECOG performance status 1, and 58.5% were never smokers. At baseline 43.4% of

patients had central nervous system (CNS) disease. The safety-evaluable population included 134 patients who received ≥1 dose of entrectinib and had at least 6 months of follow-up. Patient characteristics were similar in this cohort, with the exception that more (50.0%) patients had CNS disease at baseline. The primary endpoints of all studies were objective response rate (ORR) and duration of response (DoR). Key secondary endpoints included progression-free survival (PFS) and safety. Additional endpoints were intracranial ORR (complete response [CR]), plus partial response [PR]), DoR in patients with intracranial response, and PFS in patients with or without baseline CNS disease.

Patients with and without CNS disease at baseline showed clinically meaning benefit following entrectinib; the ORR was 77.4% in the overall population and included 3 (5.7%) patients with CR. The DoR was 24.6 months. The clinical benefit rate was 77.4%. Patients with CNS disease at baseline showed an ORR of 73.9%, but no CR was observed. The median DoR was 12.6 months. Median PFS in the overall and CNS-positive cohorts was 19.0 months and 13.5 months, respectively. The overall survival data were not yet mature with a median follow-up of 15.5 months.

The intracranial ORR by BICR assessment was 55%; CR was achieved by 4 (20%) patients, and PR by 7 (35%) patients but no stable disease was observed. Disease progression occurred in 15% of patients and 30% of patients were non-evaluable. In patients showing an intracranial response, the median DoR was 12.9 months.

In the ROS1 safety-evaluable population at least one treatment-related adverse event (TRAE) of any grade was seen in 93% of patients. The most commonly reported TRAEs were dysgeusia (42.5%), dizziness (32.8%), and constipation (32.8%%). TRAEs grade ≥3 included weight gain, which occurred in 7.5% of patients, diarrhoea in 2.2%, myalgia and aspartate aminotransferase increase occurred in 1.5% of patients each, dysgeusia, dizziness and creatinine increase each occurred in 0.7% of patients. There were no grade 5 TRAEs. TRAEs led to dose reduction or discontinuation in 34% and 5% of patients, respectively. ALKA-372-001 (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267). Barlesi *et al.* Abstract 109O

Practice point and future research opportunities

There are high unmet needs for treatment options in patients with ROS1 fusion-positive NSCLC. Brain metastases are common in this population and the CNS is a common site of first progression. Entrectinib is a potent ROS1 inhibitor that also inhibits TRKA/B/C that was designed to cross the blood-brain barrier and effectively penetrate the CNS to achieve therapeutic levels in the CNS.

These findings show that entrectinib is highly active in patients with ROS1-positive NSCLC with and without CNS disease; entrectinib demonstrated clinically meaningful deep and durable systemic and intracranial responses. High response rates were observed with entrectinib treatment in patients with ROS1-positive NSCLC.

Entrectinib is especially active in patients with NTRK fusion-positive non-small cell lung cancer with and without brain metastasis

Luis Paz-Ares of the Hospital Universitario Doce De Octubre, in Madrid, Spain explained that entrectinib is a potent inhibitor of TRKA/B/C and ROS1 that also is active in the central nervous system (CNS). Entrectinib has activity in several histologies since it targets the chimeric TRK proteins, which have constitutively activated kinase function that provide oncogenic potential across several tumour types. TRK proteins are the gene products of neurotropic receptor tyrosine kinase (*NTRK*) gene fusions; therefore, the STARTRK-2, STARTRK-1 and ALKA-372-001 trials enrolled 54 patients with 10 tumour types, and more than 19 histopathologies with locally advanced/metastatic NTRK fusion–positive solid tumours to evaluate the efficacy and safety of entrectinib. The patients' median age was 57.5 years (range, 21 to 83 years) and 59.3% were female. The trials evaluated the disease burden per blinded independent central review (BICR) using RECIST v1.1, after the first 4-week cycle and every 8 weeks thereafter. The primary endpoints included objective response rate (ORR) and duration of response (DoR) by BICR, while progression–free survival, (PFS), overall survival (OS), and safety served as the secondary endpoints.

Although responses were observed across all tumour types, professor Paz-Ares focused on the results from an analysis of 10 patients with non-small cell lung cancer (NSCLC) who demonstrated an ORR of 79% with entrectinib, compared to an ORR of 57.4% in the overall population. The NSCLC cohort also demonstrated a median DoR of 10.4 months, median OS of 20.9 months, and median PFS of 11.2 months. In the 6 patients with NSCLC who also had brain metastases, 4 experienced an intracranial response comprised of 2 complete responses and 2 partial responses; in this cohort, one patient achieved stable disease and one patient was not evaluable.

The safety profile for entrectinib in the NSCLC patients was also similar to that of the overall population, which consisted of 68 patients with NTRK fusion–positive solid tumours who received at least 1 dose of entrectinib. Mostly grades 1-2 treatment-related adverse events (TRAEs) were reported; grade 3 TRAEs occurred in 32.4% of patients and grade 4 TRAEs in 2.9%. No grade 5 TRAEs occurred but 4.4% of TRAEs led to study drug discontinuation and dose reductions in 39.7% of patients. ALKA-372-001 (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267). Paz Ares *et al.* Abstract 113O

Practice point and future research opportunities

This integrated analysis of global multicentre clinical trials demonstrated that entrectinib induced clinically meaningful, durable responses that were both systemic and intracranial in patients with NTRK fusion–positive solid tumours. Entrectinib was particularly effective in NTRK fusion–positive NSCLC and in patients who also have central nervous system disease.

Activity of larotrectinib in TRK fusion lung cancer

Alexander Drilon, Memorial Sloan Kettering Cancer Centre, New York, USA discussed findings from the cohort of patients with lung cancer enrolled in a trial of the tropomyosin receptor kinase (TRK) inhibitor, larotrectinib. According to previously reported data from the trial, larotrectinib demonstrated an overall response rate (ORR) of 75% by independent central review across a broad range of tumour types.[1] At ELCC 2019, findings from the subset of 11 lung cancer patients with tumours harbouring TRK fusions treated with larotrectinib in two clinical trials were reported. Larotrectinib was administered at 100 mg twice daily on a continuous 28-day schedule until withdrawal, unacceptable toxicity, or disease progression occurred. The patients' median age was 52 years (range, 25 to 76). Prior systemic therapy had been received by 10 patients, with 5 patients undergoing 3 or more previous therapies. The best response to the last therapy in these patients was one partial response (PR) and 4 patients with stable disease (SD).

TRK fusion was determined by molecular profiling; 8 patients had fusions involving NTRK1 and diverse fusion partners, including EPS15 in 2 patients, TPM3 in 2, IRF2BP2 in 2, and one patient each had an NTRK1 fusion with TPR, and SQSTM1. Three patients had fusions involving NTRK3; of these, the fusion partner was SQSTM1 in 2 patients, and ETV6 in one patient.

Of the 11 larotrectinib treated patients, 7 had evaluable data and 4 patients had been on treatment less than one month and were non-evaluable for efficacy. One complete response, 4 PR, and 2 SD were observed, yielding an ORR of 71%. The response was relatively quick, with a median time to response of 1.8 months. The median duration of response was not reached (range, 7.4+ to 17.6+ months). Two patients discontinued treatment due to disease progression and one withdrew consent.

Larotrectinib was well tolerated. Treatment related adverse events were mostly grades 1 and 2. NCT02122913, NCT02576431. Drilon *et al.* Abstract 111O

Citation:

1. Drilon A, *et al*. *NEJM* 2018; 378:731-9.

Practice point and future research opportunities

Larotrectinib is the first FDA-approved selective TRK inhibitor; these findings show that larotrectinib is highly active in lung cancer patients harbouring NTRK gene fusions. These results strongly support the inclusion of NTRK gene fusions as part of routine molecular testing for patients with lung cancer and further study of larotrectinib in patients with TRK fusion-positive lung cancer.

Low detection rate of genomic alterations as assessed by plasma circulating tumour DNA in patients with advanced non-small cell lung cancer and isolated central nervous system metastases

Michaela Aldea, Medical Oncology, Gustave Roussy Institute, Villejuif, France and colleagues evaluated the role of circulating tumour DNA (ctDNA) in molecular profile testing at diagnosis of non-small cell lung cancer (NSCLC) and upon developing resistance to targeted therapies in patients with central nervous system (CNS) metastasis. Their retrospective analysis assessed the feasibility of using ctDNA in consecutive patients treated for NSCLC and isolated CNS disease (iCNS) and/or progression at the Institut Gustave Roussy from January 2016 to June 2018. From this review, the investigators selected patients having any molecular tissue alteration at baseline including EGFR, ALK, BRAF, KRAS, HER2, ROS1, MET, TP53, plus CNS disease and ≥1 ctDNA samples at diagnosis and at progression. The ctDNA analysis was performed by next generation sequencing (NGS- InVisionSeq™-Lung) and ctDNA was defined as positive if ≥1 mutation in the NGS panel was detected. The ctDNA data in the iCNS group were compared to the group of patients with systemic disease and progression.

Of the 959 screened patients, 422 had ≥1 ctDNA sample and 183 of these patients also had CNS disease. Among these patients, 58 had a ctDNA sample at the time of CNS disease and 66 samples were eligible for inclusion; 21 samples were iCNS and 45 were systemic-CNS. In the cohorts of patients with iCNS and systemic-CNS, the median age was 55 and 59 years, 94% and 59% of patients were female, and adenocarcinoma histology was present in 100% and 93% of patients, respectively. In the respective cohorts, 35% versus 44% of patients had a smoking history, and the median number of mutated sites at diagnosis was 1 versus 2. The prevalence of EGFR mutation at diagnosis was 76% and 61%, ALK rearrangement was observed in 18% and 10% of patients, KRAS in 6% and 5% in iCNS and in systemic CNS patients, respectively. Alterations of HER2, TP53, BRAF and MET were present only in the systemic-CNS group at an incidence of 12%, 10%, 5%, and 2%, respectively.

ctDNA was positive in 38% of patients with iCNS, compared to 98% in systemic-CNS (Fisher test, $p < 0.0001$). Targetable genetic alterations were detected in 20 versus 40 patients in the respective cohorts. Patients in the iCNS cohort had metastasis to the brain (62%), and meninges (38%), but no patients had both. Aldea *et al.* Abstract 110O

Practice point and future research opportunities

Patients with NSCLC and isolated CNS involvement had a low detection rate of genomic alterations as assessed by ctDNA in plasma, compared to patients with systemic CNS involvement, where the detection rate was 98%. ctDNA in plasma remains an effective tool in patients with systemic CNS involvement, but is feasible in patients with isolated CNS involvement.

Circulating tumour DNA analysis tracks development of resistence mutations and response following ensartinib in patients with ALK-positive non-small cell lung cancer

Leora Horn, Department of Medicine, Vanderbilt University Medical Centre in Nashville, USA, and colleagues performed the study to identify resistance mutations that develop following successful treatment with ALK inhibitors. The investigators assessed the utility of circulating tumour DNA (ctDNA) analysis in monitoring treatment response longitudinally and in detecting resistance mutations during ensartinib therapy. They collected blood samples upon initiation and during ensartinib treatment from patients participating in the eXalt2 trial. DNA from plasma samples was hybridised to a panel of probes using the Resolution Biosciences targeted hybrid-capture system. In addition, archival tumour tissue from a subset of patients was analysed for comparison. Efficacy assessments included response rate (RR) and median progression-free survival (PFS).

As of 1 April 2018, baseline plasma samples from 76 patients treated with entrectinib for ALK-positive non-small cell lung cancer (NSCLC) had been analysed. Twenty-two percent of these patients were naive to ALK tyrosine kinase inhibitors (TKIs), 49% had received prior crizotinib, and 29% had received crizotinib plus ≥1 second-generation ALK TKI. A high concordance rate (91%) was observed between the plasma and tissue analyses of ALK fusions. Of the 69 patients evaluable for efficacy, 17 (24%) patients had the EML4-ALK variant 1 (V1), 7 (10%) patients had V3 at baseline, and 12 (17%) patients had non-V1 or non-V3 fusions.

The investigators noted that both the RR and median PFS with ensartinib were more favourable in the 9 patients having V1 compared to the 1 patient with V3 fusions, where the RR was 53% versus 14%, respectively and median PFS was 8.2 versus 1.9 months. The RR in 7 patients with other EML4-ALK variants was 58%.

The longitudinal plasma samples that were analysed in 11 patients showed that reduced allelic frequencies of ALK fusions were detected over the course of clinical response to entrectinib, which was followed by increased numbers of ALK fusions and/or the emergence of new mutations in ALK at or before disease progression. NCT01625234. Horn *et al.* Abstract 112O

Practice point and future research opportunities

The results of this study suggest that plasma ctDNA analysis can potentially be used to identify a subgroup of patients with ALK-positive NSCLC who may derive clinical benefit from ensartinib. Furthermore, serial assessments of ctDNA during therapy offer a convenient, non-invasive method to track tumour response and to define the mutational landscape of acquired resistance.

Lower dose of osimertinib is effective for patients with leptomeningeal metastases and EGFR-mutated advanced non-small cell lung cancer

Myung-Ju Ahn, Department of Haematology-Oncology, Samsung Medical Centre-Sungkyunkwan University School of Medicine in Seoul, Republic of Korea reviewed data from the BLOOM trial, which demonstrated efficacy in patients with leptomeningeal metastases (LM) and non-small cell lung cancer (NSCLC) following treatment with osimertinib at 160 mg once daily. Professor Ahn and colleagues evaluated osimertinib, a 3rd-generation EGFR tyrosine kinase inhibitor (TKI) that is selective for both sensitising and EGFR T790M resistance mutations, at half that dosing level in patients with LM. Patients with EGFR T790M-positive advanced NSCLC and progression on an EGFR TKI, as well as LM confirmed by neuro-radiological blinded independent review (BICR) and CNS metastases were eligible if asymptomatic and stable to participate in the 4 trials of the AURA programme. This analysis comprised 22 patients who were treated with osimertinib at 80 mg one daily in the AURA trials. Following treatment, brain scans were assessed for radiologic LM response by BICR per Response Assessment in Neuro-Oncology LM criteria. A longitudinal analysis compared changes from baseline in non-CNS (non-central nervous system) tumour size with LM responses at each visit for AURA LM and BLOOM LM patients.

The patients baseline characteristics in the lower dose cohort were broadly consistent with those of the overall AURA study population. The median age was 58 years, 59% of patients were female 82% were Asian, and the majority (82%) of patients were WHO performance status 1. The LM objective response rate (ORR), LM duration of response (DoR), LM progression-free survival (PFS), and overall survival (OS) were retrospectively evaluated.

After treatment exposure of a median 7.3 months (range, 2.3 to 16.5 months), the LM ORR was 55%, and 6 (27%) patients each achieved complete or partial LM response. The median LM DoR was not reached. The median LM PFS was 11.1 months and median OS was 18.8 months. Graphical assessment of longitudinal analysis showed similar non-CNS and LM responses in AURA LM and BLOOM LM patients. AURA extension (NCT01802632), AURA2 (NCT02094261), AURA3 (NCT02151981), AURA17 (NCT02442349). Ahn *et al.* Abstract 105O

Practice point and future research opportunities

The results of patients treated with osimertinib at 80 mg daily were consistent with early efficacy outputs from the BLOOM trial, where patients received osimertinib at 160 mg daily. At the lower dose, osimertinib showed a clinically meaningful benefit in patients with T790M-positive NSCLC and radiographically-detected LM.

However, additional study is necessary to further evaluate the CNS efficacy of osimertinib at 80 mg per day in patients with EGFR-mutated NSCLC and LM.

Next generation sequencing used to evaluate potential resistance mechanisms to osimertinib in EGFR T790M-positive non-small-cell lung cancer

Chunwei Xu, Pathology, Fujian Cancer Hospital, Fuzhou, China and colleagues used next generation sequencing (NGS) to characterise the mutational and genetic status of patients treated with osimertinib, which has shown significant clinical benefit in patients with non-small cell lung cancer (NSCLC) plus EGFR sensitising mutations or T790M mutation. They aimed to determine the underlying factors in primary resistence to osimertinib, which is seen in approximately 5% to 15% of patients with NSCLC and EGFR T790M mutation. Their study contained 117 patients with stage IIIb-IV EGFR T790M NSCLC who provided tumour biopsies, including FFPE samples, serum samples, and serous effusions. The rate of acquired osimertinib resistence in these patients was 82.91%, and 7.69% of patients showed primary resistance.

Among these patients, analysis of baseline specimens revealed that 3 (33.33%) patients had MET amplification, and one (11.1%) patient each had BCL2L11 loss (BIM deletion polymorphism), ERBB2 amplification, PTEN mutation, and EZH2 mutation; two (22.22%) patients had unknown status. Xu *et al.* Abstract 114O

Practice point and future research opportunities

Analysis of the baseline mutational status in patients with NSCLC and T790M mutation who also had primary or acquired resistence to osimertinib suggest that the mechanisms of primary resistance to EGFR T790M may be highly heterogeneous and may involve BCL2L11 loss, MET amplification, ERBB2 amplification, PTEN mutations, or EZH2 mutations. Several genetic mutations may contribute to the molecular mechanisms of primary resistance to osimertinib in EGFR T790M NSCLC. Further investigation of the mechanism of resistance to osimertinib is necessary.

Afatinib shows clinical benefit in EGFR TKI-naïve patients with locally advanced/metastatic non-small cell lung cancer harbouring EGFR mutations

Antonio Passaro of the European Institute of Oncology in Milan, Italy, remarked that chemotherapy remains the first-line treatment in patients with advanced/metastatic non-small cell lung cancer (NSCLC) harbouring EGFR mutations in real-world clinical practice despite the demonstration in clinical trials of significantly improved progression-free survival (PFS) compared to chemotherapy in this patient population. In the LUX-Lung-3 and -6 trials the median PFS was 11.1 with afatinib versus 6.9 with chemotherapy (hazard ratio [HR] 0.58) and 11.0 with afatinib versus 5.6 months with chemotherapy (HR 0.28), respectively. Afatinib also outperformed gefitinib in LUX-Lung-7 by demonstrating median PFS of 11.0 versus 10.9 months, respectively (HR 0.73). Adding to the data on afatinib, professor Passaro presented findings on behalf of colleagues from an interim analysis of a phase IIIb study of afatinib in patients with EGFR mutation-positive advanced/metastatic NSCLC and ECOG performance status (PS) 0–2, who were either treatment-naïve or pre-treated with

chemotherapy. This study was conducted similarly to real-world practice, with EGFR tyrosine kinase inhibitor (TKI)-naïve patients treated with afatinib at a starting dose of received 40 mg/day. Dose reduction to a minimum of 20 mg/day was permitted. The primary endpoint was descriptive adverse events (AEs) and efficacy was also assessed.

At data cut-off on 30 April 2018, the study comprised 479 patients; they were primarily (97%) Caucasian, 66% of patients were female, and ECOG PS was 0, 1, or 2 in 36%, 57%, and 8% of patients, respectively. Seventeen percent of patients had baseline brain metastases, 87% of patients had common mutations, and 13% of patients had uncommon mutations. Afatinib had been administered as first-, second- or third-line in 78%, 17%, and 5% of patients. Median duration of afatinib treatment was 359 days.

The most commonly reported grade ≥3 afatinib-related AEs were diarrhoea in 16% and rash in 11% of patients. Dose reduction due to an AE was reported for 258 (54%) patients, and afatinib discontinuation occurred in 105 (22%) patients. Afatinib-related serious AEs occurred in 39 (8%) patients.

Following afatinib therapy, the objective response rate was 46% and the disease control rate was 86%, the median time to symptomatic progression (TTSP) was 14.9 months and median PFS was 13.4 months. NCT01853826. Passaro *et al.* Abstract 115O

Practice point and future research opportunities

Findings from the interim safety analysis suggest that afatinib has a predictable and manageable safety profile that is consistent with the pivotal LUX-Lung trials. In addition, the interim efficacy results are encouraging, with a median TTSP of 14.9 months in patients receiving in first- and later lines, including those with ECOG PS 2, brain metastases and/or uncommon mutations.

Health-related quality of life remains stable or improves during 12 months of real life nivolumab treatment for non-small cell lung cancer

Maurice Perol of the Centre Léon Bérard in Lyon, France and colleagues conducted the EVIDENS study, an observational, prospective, multicentre cohort study that monitored lung cancer patients initially treated with nivolumab from October 2016 to November 2017 in 146 French centres. Professor Perol discussed temporal changes in heath-related quality of life (HRQoL) in this real-world study, which provided interim efficacy and safety results that were consistent with findings from nivolumab clinical trials. The study comprised 1,394 patients with non-small cell lung cancer (NSCLC) whose treatment was followed-up for a median of 11.5 months. HRQoL was measured using the EQ-5D-3L, a 3-level version consisting of the 5 dimensions descriptive system (EQ-5D) and the visual analogue scale (VAS; 0–100 [worst–best health]). Outcomes for each dimension were described as the proportion of patients showing no change, improvement or deterioration, the utility index and VAS mean

changes from baseline were reported with minimally important difference [MID] set at 0.08 and ±7 point change, respectively).

The median age of the patients was 66.0 years, 69.2% were men, 89.6% were current or former smokers, and 83.2% were ECOG performance status 0-1, and 31.1% of patients had squamous histology. The baseline completion rates for EQ-5D-3 were 80.2% and 77.0% for the VAS. At 9 and 12 months, 276 and 78 patients were at risk, respectively. At 9 months, according to the EQ-5D-3L scale most (75.4%) patients reported unchanged mobility, 85.2% reported unchanged self-care, 58% reported unchanged anxiety or depression, and 63.4% of patients reported unchanged pain or discomfort.

At 12 months unchanged status in these categories was reported by 81.5%, 94.4%, 66.7%, 70.4%, and 55.6% of patients, respectively. The increases in patients reporting an unchanged status derived mostly from patients who had previously described their status as deteriorating from baseline; for example, 14.1% of patients reported deteriorating mobility at 9 months but only 7.4% reported poorer mobility at 12 months. Deteriorating self-care are 9 and 12 months was reported by 8.5%, and 3.7% of patients, respectively. Deterioration from baseline for anxiety/depression was reported by 16.2% versus 13.0% patients and deterioration in pain/discomfort was reported by 14.1 versus 13.0% of patients at 9 and 12 months, respectively. Of note, the mean changes of VAS from baseline were statistically significant at 9 and 12 months regardless of histology, and MID was achieved at 12 months for patients with squamous histology (+7.6; 95% confidence interval [CI], 2.1-13.1). NCT03382496. Perol *et al.* Abstract 118O

Practice point and future research opportunities

Quality of life questionnaires following 12 months of nivolumab treatment reflected improvement across all 5 dimensions measured by EQ-5D-3L, with the majority of patients reporting stable status; in addition, a clinically meaningful improvement of VAS was observed in patients with squamous histology.

Racial disparities are determined in patient characteristics and prognosis in Asian versus White patients treated with atezolizumab

Using data from the POPLAR and OAK studies Jei Qian, Pulmonary Medicine, Shanghai Chest Hospital, Shanghai, China and collegues assessed the differences of ethnicity across baseline characteristics, outcomes, and genetic mutations following atezolizumab therapy. Their study cohort included 390 patients who received atezolizumab and had evaluable biomarker parameters retrieved from a subsequent blood-based study.

The investigators found that Asiatic and White patients differed in baseline characteristics including smoking history, tumour baseline sum of the longest diameters (BLSLD), EGFR mutation frequency, programmed death-ligand 1 (PD-L1) expression, and blood-based tumour mutational burden (bTMB) levels. Regarding outcome, overall survival (OS) was

longer in Asians compared with Whites before propensity score matching (PSM; median OS was 18.7 versus 11.1 months; p = 0.005) as well as after PSM (median OS 20.9 versus. 12.6 months; p = 0.005), prompting the investigators to conclude that race was an independent prognostic factor for OS; for the comparison of Asian versus White race, hazard ratio (HR) 0.647; p = 0.021).

The objective response rates for Asians and Whites were 8.2% versus 17.1%, and disease control rates were 51.2% versus 47.7%, respectively. Performance status, histology, BLSLD, and the number of metastatic sites were also found to be independent prognostic factors for OS.

The blood-based mutational landscape also differed between Asians and Whites. In the overall population, mutations of *STK11, EGFR, KEAP1, POLE, GRM3, ATM* and *STAG2* were associated with treatment response while mutations of *TP53, KEAP1, APC, RB1, CREBBP, EPHA5,* and *STAG2* were associated with OS. Comparing the frequency of efficacy- or prognosis- related mutations, Asians had more *EGFR* mutations, but fewer *TP53* and *STK11* mutations than Whites. Qian *et al.* Abstract 117O

Practice point and future research opportunities

Asians and Whites differed in the clinicopathological features and mutational landscape, which may explain longer overall survival with atezolizumab observed in Asiatic patients with NSCLC. This study conveys implications for further studies on racial disparity in the treatment of immunotherapy.

Low blood tumour mutational burden predicts clinical benefit in non-small cell lung cancer patients treated with docetaxel

W. Nie of the Shanghai Chest Hospital, Shanghai, China and colleagues evaluated the blood-based tumour mutational burden (bTMB) as a predictive biomarker for non-small cell lung cancer (NSCLC) patients receiving chemotherapy. An association between high bTMB and atezolizumab response had been determined, leading the investigators to test whether low bTMB may correlate with better chemotherapy response in patients with advanced NSCLC. Using the clinical and genetic data from 318 patients in the docetaxel arm of the OAK trial and 106 patients in the POPLAR validation cohort, the investigators used the FoundationOne CDx next generation sequencing assay to quantify bTMB. Efficacy was determined by RECIST v1.1 and durable clinical benefit (DCB) was defined as overall survival (OS) lasting more than 12 months. Gene alterations and bTMB were compared in patients demonstrating DCB and patients showing no durable benefit (NDB). The cut-off value of bTMB for predicting OS was determined by time-dependent receiver operating characteristic (ROC) curve.

Significantly lower bTMB was observed in patients demonstrating DCB than those with NDB; the median bTMB was 5 versus 9 SNVs/Mb (p < 0.001). Lower bTMB was also

observed in patients achieving partial response or stable disease compared to those experiencing progressive disease; median bTMB was 5 versus 7 versus 10 SNVs/Mb, respectively (p = 0.007).

The optimised cut-off value of bTMB for predicting OS was 7 SNVs/Mb by time-dependent ROC curve. Median OS in patients with low bTMB in the training cohort was 11.5 months compared to 6.4 months for those with high bTMB (hazard ratio [HR] 0.638; p < 0.001). Median progression-free survival in the low bTMB group was 4.3 months compared to 2.9 months in the high bTMB group (HR 0.588; p < 0.001). These results were confirmed by testing in the validation cohort. In addition, the investigators determined that variants in EGFR and KEAP1 associated with DCB and variants in KEAP1 associated with NDB. Nie *et al.* Abstract 118O

Practice point and future research opportunities

In this analysis, low bTMB defined by a cut-of value of ≤ 7 SNVs/Mb was a clinical biomarker of response to docetaxel treatment in NSCLC. Patients with low bTMB derived greater benefit from docetaxel chemotherapy as compared to patients with high bTMB, who showed greater clinical benefit from atezolizumab.

Nintedanib plus docetaxel combination provides patient benefit and is safe following second-line immune checkpoint inhibitor treatment for lung adenocarcinoma

Nintedanib, a triple angiokinase inhibitor of VEGF-, PDGF- and FGF-receptors, has been approved in the EU and elsewhere for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) of adenocarcinoma histology when administered in combination with docetaxel after first-line chemotherapy. Nevertheless, efficacy and safety data remain sparse for nintedanib in patients that have received prior immune checkpoint inhibitors (ICIs) for NSCLC, according to Christian Grohe, Department of Pneumology, ELK Berlin, Berlin, Germany. He presented findings from an interim analysis of 22 patients with locally advanced or metastatic stage IIIB/IV lung adenocarcinoma in cohort B of the VARGADO study who received oral nintedanib plus docetaxel as third-line line following second-line ICIs. VARGADO is an ongoing non-interventional study; cohort B comprised 22 patients with a median age of 58 years (range, 45 to 76). The majority of patients (68.2%) were men, 72.7% were ECOG performance status 0/1,18.2% had brain metastases at baseline, and 86.4% of patients were current or former smokers. First-line chemotherapy with pemetrexed had been administered to 68.2% of patients, 54.6% received carboplatin, 54.6% had received cisplatin, 27.3% bevacizumab, 18.2% vinorelbine, 9.1% paclitaxel, and 4.4% of patients had received docetaxel. Second-line treatments included nivolumab in 77.3%, or pembrolizumab in 22.7% of patients.

The efficacy analysis comprised 12 patients. Following third-line nintedanib and docetaxel, 7 (58.3%) patients achieved partial response and 3 (25.0%) patients showed stable disease for a disease control rate of 83.3%. The median progression-free survival was 5.5 months.

Of the 22 patients in the safety cohort, treatment emergent adverse events (TEAEs) grade ≥3, serious TEAEs, and TEAEs leading to discontinuation were observed in 59.1%, 50.0%, and 31.8% of patients, respectively. NCT02392455. Grohe *et al.* Abstract 119O

Practice point and future research opportunities

The combination of nintedanib and docetaxel administered after first-line chemotherapy and second-line immune checkpoint inhibitor therapy showed clinically relevant efficacy and an adequate safety profile in patients with stage IIIB/IV lung adenocarcinoma Further studies are justified to fully explore the potential of nintedanib and docetaxel in this setting, which may confirm an anti-angiogenesis agent plus docetaxel as a subsequent therapeutic principle in patients progressing on immunotherapy.

MESOTHELIOMA

Tumour Treating Fields in combination with chemotherapy improve survival in unresectable malignant pleural mesothelioma

Giovanni Luca Ceresoli, Department of Medical Oncology, Humanitas Gavazzeni in Bergamo, Italy discussed the phase II STELLAR trial of Tumour Treating Fields (TTFields) in addition to chemotherapy in patients with unresectable malignant pleural mesothelioma. TTFields is a regional treatment that utilizes low intensity, alternating electric fields delivered non-invasively to the tumour using a portable medical device. TTFields have already been approved for patients with glioblastoma.

Eighty patients with unresectable, previously untreated mesothelioma participated in the trial and received continuous 150 kHz TTFields for more than 18 hours per day in combination with pemetrexed and cisplatin or carboplatin. The patients were required to have ECOG performance status (PS) of 0-1 and pathologically proven mesothelioma. A visual analogue scale was used to assess ECOG PS and cancer-related pain was assessed until disease progression. The sample size was planned to provide 80% power with two-sided alpha of 0.05 to detect an increase in median OS of 5.5 months for a comparison to historical controls (Vogelzang, JCO 2003). The patients' median age was 67 years (range, 27 to 78), 84% were male, 44% of patients had an ECOG PS of 1 and the remainder had ECOG PS 0. Similar to the historical control, 66% of patients had epithelioid histology. Overall survival (OS) served as the primary endpoint.

All 80 patients received treatment and were followed-up for a minimum of 12 months. Median OS was 18.2 months compared to 12.1 months in the historical control, thus meeting the primary endpoint. Patients with epithelioid histology had a median OS of 21.2 months. The patients' ECOG PS remained stable during the first year of follow up; median time to deterioration in PS was 13.1 months. The average pain score was lower compared to baseline during the first 7 months of the treatment but increased later on the study; the median time to a clinically significant 33% increase in pain was 8.4 months.

No device-related serious adverse events were reported. As expected, TTFields-related dermatitis was reported in 46% of patients and 4 patients (5%) had grade 3 dermatitis. NCT02397928. Ceresoli *et al.* Abstract 196O

Practice point and future research opportunities

The study met the primary endpoint of significantly prolonged overall survival, especially in patients with epithelioid histology, compared to a historical control in patients with previously untreated mesothelioma. The TTFields treatment was not associated with a decrease in ECOG PS or an increase in pain for the duration of TTFields use. TTFields in combination with chemotherapy warrants additional study in this patient population.

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Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

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