

2017 EUROPEAN LUNG CANCER CONFERENCE (ELCC)

5-8 May 2017

Geneva, Switzerland

Table of Contents

Summary	4
INTRODUCTION	5
TUMOUR BIOLOGY AND PATHOLOGY	7
ROS1 immunocytochemistry on cytological specimens may be useful as preliminary screen for ROS1 rearrangements in patients with NSCLC	7
Specific immune cell profiles address tumour immune escape and may identify lung cancer patients responsive to anti-PD-1 immunotherapy	7
Negative indicators of response to treatment identified in EGFR mutant NSCLC	10
TRANSLATIONAL RESEARCH	11
White blood cell count predicts response to nivolumab in patients with NSCLC	11
SMALL CELL LUNG CANCER (SCLC)	13
Improved long-term survival with chemoradiotherapy plus prophylactic cranial irradiation in patients with early limited-stage SCLC	13
Systematic literature review of second- and third-line treatments used for SCLC	14
EARLY STAGE NSCLC	15

Literature meta-analysis shows similar disease-free survival following resection of NSCLC in patients with mutated EGFR compared to wild-type	15
Confirmation of the benchmark of examined lymph node count in patients with node positive NSCLC using the SEER database	16
LOCALLY ADVANCED NSCLC	17
Patient data used for evaluation of radiation-induced lung toxicity prediction modelling in NSCLC.....	17
ADVANCED NSCLC.....	19
Encouraging clinical benefit with atezolizumab in patients with advanced NSCLC with or without baseline brain metastases	19
Durable responses demonstrated with durvalumab in heavily pretreated patients with metastatic EGFR-mutated/ALK-positive NSCLC: ATLANTIC study results	20
Durvalumab provides meaningful clinical benefit and durable responses in patients previously treated for stage IV squamous NSCLC	21
First-line atezolizumab monotherapy shows long term efficacy in PD-L1–selected patients with NSCLC: Update from the BIRCH	22
Symptom amelioration with osimertinib according to patient reported outcomes in advanced NSCLC.....	23
Ensartinib demonstrates clinical benefit in patients with ALK-positive NSCLC and CNS metastases.....	25
Patients with NSCLC that have been pre-exposed to PD-1/PD-L1 inhibitors demonstrate greater response to salvage chemotherapy	27
Prospective study shows the cobas [®] test can detect EGFR mutation in plasma ctDNA with good concordance between ctDNA and tumour samples	28
Brigatinib demonstrates greater than 50% confirmed response in patients with crizotinib-refractory ALK-positive NSCLC: Updates from the ALTA trial.....	31
The development of brain metastases in molecular selected and wild-type patients with NSCLC included in clinical trials	32
Cancer patients on immunotherapy may be a greater risk of complications from influenza vaccine.....	33

Expanded RNA and protein-based testing detects actionable biomarkers in driverless lung carcinoma 35

METASTASES TO AND FROM THE LUNG 36

 The molecular status of the tumour associates with the anatomic sites of metastases at diagnosis of NSCLC..... 36

 EGFR-mutation testing by ctDNA in plasma is more sensitive in patients with extrathoracic disease..... 36

 PD-L1 expression patterns in metastatic tumours to the lung compared with primary NSCLC 37

RELATED INFORMATION 39

Affiliations and Disclosure..... 40

 Affiliation 40

 Disclosure 40

Acknowledgement 41

Summary

The seventh edition of the European Lung Cancer Conference (ELCC) welcomed 1'964 medical and healthcare professionals from around the world who gathered to discuss the latest developments in the quickly changing landscape of lung cancer research and clinical practice. The abstracts chosen for presentation and discussion represented 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 2017 follows.

INTRODUCTION

The seventh edition of the European Lung Cancer Conference (ELCC) welcomed 1'964 medical and healthcare professionals from around the world who gathered to discuss the latest developments in the quickly changing landscape of lung cancer research and clinical practice.

The conference was attended by 1'612 delegates, including 226 exhibitors and industry representatives, 104 faculty members, and 20 members of the press. Although the highest proportion of delegates (10.9%) represented the host country, Switzerland, the participants came from 84 different countries world-wide, including 10.1% of delegates from locations throughout the United States, 8.6% from the United Kingdom, and 5.2% of delegates travelling from China. Approximately 3% of delegates each came from Belgium, Spain, Italy, and Poland. In addition to Europe, participants represented Asia, North and South America, Africa, and Australia and the Pacific.

The majority (31%) of participants were medical oncologists, but ELCC 2017 attendees also comprised 8.3% medical staff, 7.5% pneumologists, 5.9% radiation oncologists, 4.3% surgical oncologists, and 2.7% chest physicians, as well as other medical professionals, including also geneticists, basic and clinical researchers, pathologists, and general practitioners, among others. Even though the participants showed a range of interests covering the broad spectrum of oncology disciplines from basic science to palliative care, 51% of attendees indicated that chest malignancies and 49% said non-small cell lung cancer (NSCLC) were their primary areas of interest.

The 169 abstracts chosen for presentation and discussion represented cutting edge research and the most current treatment strategies in thoracic oncology that will influence patient care. Of these, an equal 10.7% were chosen for oral presentation and poster discussion, with the remainder being presented as posters, thus providing an accessible, well-rounded programme. The oral and poster discussion sessions featured faculty that placed abstract findings into clinical perspective and discussed how the results may impact the current standard of care. In addition, questions from a well-informed audience provided lively discussion in all sessions.

Advanced NSCLC was the topic of 79 abstracts while the field of tumour biology and pathology was represented by 26 abstracts. An equal 24% of abstracts each addressed the two areas of metastasis to and from the lung and prevention, early detection, epidemiology, and tobacco control. Fifteen percent of papers tackled the fields of early stage lung cancer and translational research, whereas locally advanced NSCLC and small-cell lung cancer each accounted for 10% of abstracts. Imaging and staging of cancer represented topics in 9% of abstracts, mesothelioma 6%, and the remaining abstracts targeted miscellaneous topics.

This year's ELCC also focused on the increasing number of trials currently testing combined treatments, immunotherapy and chemotherapy, and the evaluation of the many new plasma-based assays being developed for monitoring mutations in disease progression. Investigators discussed updates from the ALTA trial of brigatinib and the BIRCH trial of atezolizumab. Several sessions covered clinical trials, such as the ATLANTIC study of durvalumab and a head to head

comparison of durvalumab versus docetaxel in NSCLC, as well as, a presentation on the efficacy in CNS metastases of the second-generation tyrosine kinase inhibitor ensartinib.

A brief summary of a few of the diverse scientific findings presented at ELCC 2017 follows.

TUMOUR BIOLOGY AND PATHOLOGY

ROS1 immunocytochemistry on cytological specimens may be useful as preliminary screen for ROS1 rearrangements in patients with NSCLC

Tatjana Vlajnic and colleagues at the Institute of Pathology-University Hospital Basel in Basel, Switzerland evaluated the utility of immunocytochemistry (ICC) on cytological specimens as a preliminary screening tool for detection of ROS1 rearrangements. Although fluorescence in situ hybridization (FISH) optionally selected for by immunohistochemistry (IHC) on histological material is the gold standard for detection of ROS1 rearrangements, the identification and optimisation of predictive marker testing on cytological specimens is necessary, since non-small cell lung cancer (NSCLC) is often diagnosed by cytology alone. The investigators performed ICC using the D4D6 antibody on ethanol-fixed and previously Papanicolaou-stained specimens. The samples were obtained from 296 patients with NSCLC, and included 243 adenocarcinomas, 47 NSCLC not otherwise specified (NOS), 6 classified as 'others', and encompassing 107 specimens from the lung, 87 locoregional lymph nodes, and 102 distant metastases. The positive control was cytopsin specimens of the ROS1 expressing HCC-78 cell line; cytoplasmic staining of any intensity was considered positive.

Twelve specimens were positive for ROS1 rearrangements and were confirmed by FISH. The 284 ICC-negative cases were confirmed by FISH in 71 cases, mRNA based fusion by next generation sequencing (NGS) in 2, and by detection of another known, mutually exclusive driver mutation in 137 cases. A ROS1 rearrangement was identified by FISH in just one ICC-negative case. Therefore, ICC done on cytological specimens for detection of ROS1 rearrangements demonstrated sensitivity of 92%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 99%. Vlajnic *et al.* Abstract 10

Practice point and future research opportunities

Rearrangement of the ROS1 gene is considered a mutually exclusive oncogenic driver mutation that occurs in 1 to 2% of NSCLC. Targeted therapy has recently been approved for ROS1-positive NSCLC, making ROS1 testing a necessary part of the diagnostic routine, even though ROS1 rearrangements are relatively rare. The ICC is well suited for use as a preliminary screening method since it is cost-effective and quickly done, as compared to costly FISH, which is also technically challenging. These findings demonstrate that ROS1 ICC is a highly accurate method for detection of ROS1 rearrangements in NSCLC, making it a desirable screening option. In addition, cases with equivocal or positive findings on ICC may be confirmed by FISH or molecular tests, such as next generation sequencing.

Specific immune cell profiles address tumour immune escape and may identify lung cancer patients responsive to anti-PD-1 immunotherapy

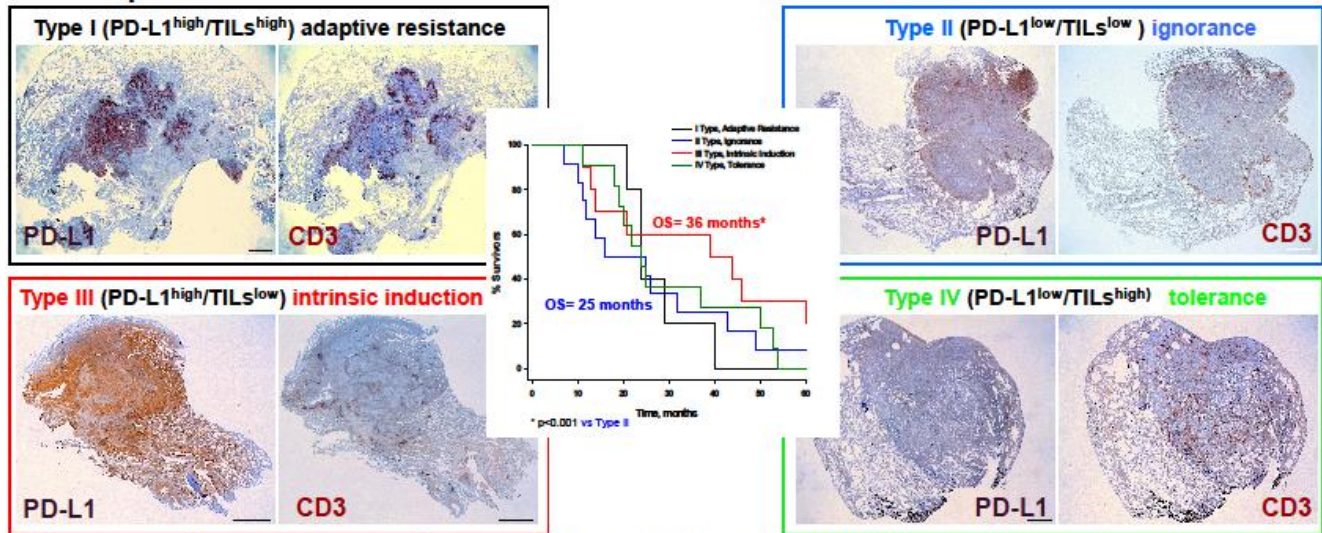
Giulia Mazzaschi, Department of Medicine, University Hospital of Parma, in Parma, Italy and colleagues conducted the study to determine the putative impact of immunologically defined classes of non-small cell lung cancer (NSCLC) on clinical outcome following immunotherapy.

The team investigated histologic sections of NSCLC samples surgically obtained from an untreated cohort of 51 patients with adenocarcinoma and 69 patients with squamous cell carcinoma (SCC) histology compared to sections from 8 patients with adenocarcinoma and 10 patients with SCC receiving nivolumab. Immunoperoxidase (H-score) and immunofluorescence were used to determine PD-L1 (clones 28-8, 22C3 and SP142) expression levels. The n/mm² and intra-, peri-tumour, and invasive margin localisation of the tumour infiltrating lymphocytes (TILs) subpopulation were computed to establish cut off values for each phenotype.

Kaplan Meier analysis of the immunohistochemical data and clinical records demonstrated that adenocarcinoma cases were 2-fold higher in CD3^{pos} and 1.8-fold lower in CD4^{pos} cells compared to SCC samples. Furthermore, patients with adenocarcinoma having a higher population of TILs in the microenvironment experienced a 10-month increase in overall survival (OS) compared to patients with low levels of TILs ($p < 0.01$). The investigators also found that the intratumoral density of TILs was lower in specimens harbouring an EGFR mutation. The frequency of type I (PD-L1^{high} TILs^{high}) contexture was low, and was observed in just 14.6% of samples in this series. Type II (PD-L1^{low/neg} TILs^{low}) was detected in more than a third of NSCLC samples, reflecting immune exhaustion. In this series, a similar proportion of type III (PD-L1^{high} TILs^{low}), with increased natural killer and granzyme B^{pos} cytotoxic cells, and IV (PD-L1^{low/neg} TILs^{high}) enriched in T-regulatory cells, immune categories was observed.

The NSCLC type III specimens showed a relationship with improved survival; patients with this type experienced median OS of 36.5 months and progression-free survival (PFS) of 27.6 months compared to OS of 25.7 months and PFS of 16.1 months in patients with type II specimens that were immune therapy naive. Patients having PD-1^{low} levels plus a high CD8/CD3 ratio showed prolonged OS of 11 months compared to patients having PD-1^{high} levels together with low CD8/CD3 ratios ($p < 0.01$). The subtype of patients with PD-L1^{high} and PD-1^{low} suggested a favourable response to immunotherapy, with 86% of these patients responding to nivolumab.

Impact of PD-L1 and TILs based Immune Contextures on NSCLC Clinical Outcome



Low magnification images of NSCLC samples immunostained for PD-L1 and CD3 as representative of the different immune contextures. Expression of PD-L1 by tumors and CD3 by TILs is shown by immunoperoxidase labeling (brownish) on serial sections from the same case.

The intimate interplay of PD-L1 mediated tumor immune escape with the number and function of Tumor Infiltrating Lymphocytes (TILs) conditions NSCLC growth and regression, markedly affecting patients OS and conceivably the response to Immune check point inhibition.



EUROPEAN LUNG CANCER CONFERENCE 2017

Impact of PD-L1 and TILs based immune contextures on NSCLC clinical outcome.

© Giulia Mazzaschi

Based on the tissue characterisation of the immune contexture and the association of specific subgroups with improved OS and response to nivolumab immunotherapy, the authors hypothesized that, in a dynamic PD-L1 milieu, a concomitant intrinsic or therapeutically induced decay of the PD-1 receptor allows TILs to escape from PD-L1 pressure and delays tumour progression, thus improving OS. Lung cancer growth and progression is attenuated by residual T lymphocyte mediated immune efficiency that can be fostered by anti-PD-1 agents. Mazzaschi *et al.* Abstract 20–

Practice point and future research opportunities

This investigation of immune cell subtypes in the tumour microenvironment of patients with lung adenocarcinoma and SCC identified an immune subgroup that associates with prolonged patient survival and may be prognostic of response to nivolumab. Based on their findings, the authors suggest that, in a dynamic PD-L1 milieu, a concomitant intrinsic or therapeutically induced decay of PD-1 receptor allows TILs to escape from PD-L1 pressure and delays tumor progression, thus improving OS. Nivolumab may augment this.

Negative indicators of response to treatment identified in EGFR mutant NSCLC

Rafael Rosell, Medical Oncology and Laboratory of Molecular Biology, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Spain and colleagues investigated the MET ligand the hepatocyte growth factor (HGF) in stromal cells, which provides an alternative signalling mechanism for the epidermal growth factor receptor (EGFR) by inducing inter-receptor cross talk with EPHA2, CUB domain-containing protein-1 (CDCP1) or AXL. Src-homology 2 domain-containing phosphatase 2 (SHP2) also plays a role in receptor tyrosine kinase (RTK) signaling and is required for MAPK activation. Therefore, the investigators assessed the expression levels of stromal HGF and levels of AXL, CDCP1, MET, EPHA2, and SHP2 expression in the tumours of 64 patients with EGFR-mutant non-small cell lung cancer (NSCLC) at baseline and following treatment with a first-line EGFR tyrosine kinase inhibitor (TKI) to find the association to clinical outcome. The discrimination between tumour and stromal cells was performed by a pathologist on paraffin-embedded samples, while mRNA expression was analysed by qRT-PCR.

AXL, CDCP1, and SHP2 emerged as the genes that most significantly influenced treatment outcome: Median progression-free survival (PFS) was 14 months in patients with high expression of AXL mRNA ($p = 0.03$) versus 23.4 months in patients with low AXL mRNA, hazard ratio (HR) 2.05 ($p = 0.03$). Median overall survival (OS) was 19.1 months ($p = 0.009$) versus 40.7 months for patients with high and low AXL mRNA, respectively, HR 2.9 ($p = 0.001$). Similarly, median PFS was 9 months ($p = 0.01$), versus 20.2 months in patients with high and low CDCP1 mRNA expression, respectively, HR 2.1 ($p = 0.02$). Median OS was 19.1 months in patients with high CDCP1 expression ($p = 0.03$) versus 34.9 months in patients with low CDCP1 mRNA, HR 2.2 ($p = 0.03$). Regarding SHP2, median PFS was 11.4 months ($p = 0.09$) versus 24 months for patients with high and low SHP2 mRNA, respectively, HR 2.4 ($p = 0.01$). Differences in OS were noted according to levels of SHP2 as well as EPHA2, and MET that did not reach statistical significance.

The PFS did not differ significantly according to levels of EPHA2 and MET in the tumour, and HGF in the stroma. Rosell *et al.* Abstract 30

Practice point and future research opportunities

According to these findings, AXL and CDCP1 are adverse predictive markers of survival and high expression levels associate with poorer PFS and OS. It has been reported that overexpression of several RTKs can substitute for EGFR signaling in EGFR-mutant NSCLC, suggesting that RTK levels should be assessed in EGFR-mutant NSCLC patients. These results also suggest that tailored combination treatment with AXL or with Src inhibitors may benefit patients with elevated CDCP1, which warrants further investigation.

TRANSLATIONAL RESEARCH

White blood cell count predicts response to nivolumab in patients with NSCLC

Lead author Marcello Tiseo, Coordinator of DMT Thoracic Oncology, University Hospital of Parma, Italy discussed findings from a study that evaluated whether white blood cell counts may be predictive of the response to nivolumab in pretreated patients with advanced non-small cell lung cancer (NSCLC). In the study, 54 patients with NSCLC were treated with nivolumab at 3 mg/kg every 14 days. White blood cell counts were obtained at baseline and following 2, and 4 cycles of nivolumab for comparison of the counts between responders and non-responders. Tumour assessment was performed after 4 cycles and every 2 months, thereafter. The percentages of lymphocyte subpopulations, including CD3, CD4, CD8, natural killer (NK; CD56) cells, and T regulatory (Treg; FOXP3) cells were assessed by FACS; these populations were also evaluated for changes in absolute number and characterised for their functional and proliferative activity. The leucocyte composition at baseline and the change during therapy were correlated with tumour response and overall survival.

Baseline Neutrophil-to-Lymphocyte Ratio, baseline NK count, lymphocyte count and CD4 variations during therapy showed a statistically significant prognostic role ($p < 0.001$; $p = 0.012$; $p < 0.001$; $p = 0.010$, respectively). Preliminary results on 31 patients having samples from all 3 time-points, showed a significant increase of NK cells and a significant decrease of CD4 percentage from T0 to T2 as well as a significant increase from T0 to T2 of the NK subpopulation CD56dim (with reduction of CD56bright). Comparison of 19 responders to 12 non-responders demonstrated an increase in NK cells (overall and of CD56dim) and a decrease in the percentage of CD4 cells, respectively; in addition, the absolute number and percent of NK cells at baseline were statistically different between the groups where the absolute number and percent of CD8-positive/PD1-positive cells at baseline were both significantly higher in responders versus non-responders. Tiseo *et al.* Abstract 30PD

Practice point and future research opportunities

Immune checkpoint inhibitors such as nivolumab and pembrolizumab significantly improve overall survival in some – but not all – patients with NSCLC, leading researchers to look for a predictive biomarker to select patients that will benefit from this treatment to avoid unnecessary toxicity and a waste of resources in patients who will not respond. The identification of markers that are predictive of immunotherapy activity remains an importance issue since the predictive role of PD-L1, as evaluated by immunohistochemistry, is debated in NSCLC. It must also be taken into consideration that small biopsies or cytological specimens often represent the only tumour material available. This study aimed to assess a circulating immuno-profile in easily obtained blood samples as predictor of the outcome from nivolumab treatment in patients with NSCLC.

This study found that white blood cell counts at baseline and during therapy predicted the outcome of nivolumab therapy; a greater number and concentration of natural killer cells at baseline was associated with response to nivolumab, as was an increase in the number of NK

cells during treatment. Responders to nivolumab also had a greater number and concentration of CD8-positive T cells that expressed PD-1. The number and function of NK cells and the frequency of PD-1 expression in CD8-positive T cells could be predictive biomarkers for nivolumab treatment in advanced NSCLC. The identification of a panel of blood predictive biomarkers would enable the early identification of patients most likely to benefit from anti-PD-1 and anti-PD-L1 treatment.

Investigation of these new factors should be included in future clinical trials, together with tumour PD-L1 expression and other markers that constitute the cancer immunogram that predicts whether or not patients will benefit from treatment.

SMALL CELL LUNG CANCER (SCLC)

Improved long-term survival with chemoradiotherapy plus prophylactic cranial irradiation in patients with early limited-stage SCLC

Ahmed Salem, Division of Molecular and Clinical Cancer Sciences, University of Manchester, Manchester, UK, presented the exploratory analysis of the phase III CONVERT trial, which compared once versus twice daily chemoradiotherapy plus prophylactic cranial irradiation (PCI). The CONVERT randomised 547 patients with limited-stage small-cell lung cancer (LS-SCLC), to radiotherapy delivered twice-daily at 45 Gy in 30 fractions over 3 weeks or to once-daily radiotherapy at 66 Gy in 33 daily fractions over 6.5 weeks. Radiotherapy using three-dimensional conformal or intensity modulated technique was initiated on day 22 of the first chemotherapy (cisplatin and etoposide) cycle in patients with good performance score (PS). PCI was offered if indicated.

The 513 patients eligible for analysis were divided into two cohorts: 87 (17%) patients had early (TNM stage I-II) disease, of these, 58.6% were male with a median age of 62 years, and 426 patients had locally advanced disease, were 53.5% male and had a median age of 62 years. The combined cohorts had Eastern Cooperative Oncology Group (ECOG) PS of 0/1 and the early cohort showed significantly lower status distribution than the locally advanced group (57.5% and 39.1% versus 43.2% and 53.8%, respectively ($p = 0.04$)). PCI use was similar between cohorts (93.9% versus 88.4%; $p = 0.142$).

In both treatment arms, median OS was doubled to 50 months in patients with early LS-SCLC versus 25 months in those with locally advanced disease ($p = 0.001$). Similarly, in both treatment arms, median time to local progression was significantly improved at 40 months in the early group compared to 17 months in the locally advanced group ($p = 0.0017$), as was the median time to metastatic progression, which was 49 versus 16 months in the early versus locally advanced groups, respectively ($p = 0.0004$).

Within the early-stage group, no significant difference was seen in median OS between treatment arms, ($p=0.31$); however, radiotherapy compliance was significantly higher in early-stage patients compared to patients with locally advanced disease ($p = 0.004$).

The incidence of acute treatment-related toxicity was similar between the early-stage and locally advanced groups. However, the early-stage group developed significantly less grade ≥ 3 acute oesophagitis (11% versus 21%; $p < 0.005$) compared to the non-early group. ISRCTN91927162, NCT00433563. Salem *et al.* Abstract 510

Practice point and future research opportunities

LS-SCLC, according to TNM staging, is a heterogeneous disease, with sparse available data to guide the management of early-stage LS-SCLC. This study guides practice for early-stage LS-SCLC patients who achieve good long-term survival with minimal acute adverse events following chemo-radiotherapy and PCI.

Systematic literature review of second- and third-line treatments used for SCLC

Rebecca Goulding, Precision Health Economics, Los Angeles, USA and colleagues conducted a systematic literature search to gather evidence and to assess the appropriate methodologies for synthesis of clinically relevant outcomes, including efficacy, safety, and health-related quality of life (HRQoL) in adult patients treated with existing second- and third-line treatments for small-cell lung cancer (SCLC), including immunotherapy, which was recently recommended in the National Comprehensive Cancer Network (NCCN) treatment guidelines for SCLC. The review was carried out using MEDLINE, EMBASE, and the Cochrane Register of Controlled Clinical Trials, as well as, manual searches of clinicaltrials.gov, the WHO International Clinical Trials Registry Platform, and 5 relevant conferences (ASCO, AACR, ESMO, WCLC, and ELCC), which were done to identify unpublished randomised clinical trials (RCTs) that were potentially eligible for inclusion. The RCTs that reported outcomes of interest, including overall survival, progression-free survival, objective response rate, and/or HRQoL for the treatments and population of interest were identified for this review. Corresponding trial, patient baseline characteristics, and outcome data were extracted for all included studies.

The review was carried out by two independent reviewers and identified 17,550 citations, including 970 conference abstracts and 25 clinical trial registry entries. Nine RCTs in SCLC were identified that investigated treatments of interest, including cisplatin, carboplatin, etoposide, amrubicin, irinotecan, gemcitabine, and topotecan; however, there were a lack of RCTs for innovative treatments such as nivolumab. Goulding *et al.* Abstract 53P

Practice point and future research opportunities

While SCLC is initially sensitive to first-line chemotherapy and radiotherapy, most patients relapse, and outcomes with second-line treatments remain bleak. Findings from this review suggest that immunotherapy, which has been recommended in the NCCN SCLC treatment guidelines for second- and third-line treatment of NSCLC, may currently be under-investigated in randomised controlled trials.

EARLY STAGE NSCLC

Literature meta-analysis shows similar disease-free survival following resection of NSCLC in patients with mutated EGFR compared to wild-type

Wenhua Liang, Department of Thoracic Surgery/Oncology, The 1st Affiliated Hospital of Guangzhou Medical University in Guangzhou, China presented findings from a meta-analysis of the literature showing the impact of epidermal growth factor receptor (EGFR) mutation on the prognosis of resectable advanced-stage non-small cell lung cancer (NSCLC) after complete surgery. Using disease-free survival (DFS) as the primary endpoint, the investigators searched electronic databases for eligible studies. The DFS was compared between EGFR mutated and wild-type patients, with special focus on stage I patients who rarely receive adjuvant therapy. In addition, DFS of patients with 19 exon deletion (19del) was compared to patients with 21 exon L858R mutation (L858R) using a random effects model.

This analysis included 13 studies and 2,652 patients. EGFR mutation was identified in 1033 (39.0%) patients; of these, 47.7% were 19del and 44.1% were L858R. Most studies used PCR-based methodology to detect EGFR mutations.

Overall, DFS in EGFR-mutated patients was similar to the DFS demonstrated in wild-type patients (hazard ratio [HR] 0.87; 95% confidence interval [CI] 0.65, 1.16) and this comparison held in the stage I subgroup for the comparison of EGFR-mutated versus wild-type patients (HR 0.82; 95% CI 0.40,1.69). A non-statistically significant trend towards inferior DFS was seen in patients with 19del compared to patients with L858R patients (HR 1.38; 95% CI 0.76, 2.52). Liang *et al.* Abstract 590

Practice point and future research opportunities

Although EGFR mutation generally represents a favourable prognostic factor in NSCLC, since it allows treatment with EGFR-tyrosine kinase inhibitors for advanced disease, the impact of EGFR mutation on the prognosis following complete surgery, of resectable NSCLC remains controversial.

This analysis uncovered no significant difference in postoperative DFS in EGFR-mutated patients compared to wild-type patients with resectable NSCLC. Therefore, there is no sufficient evidence to support different postoperative treatment strategy (especially in stage I) for mutated and wild-type patients. These findings suggest that 19del might be an adverse factor, possibly requiring more intensive management. Thus, reporting the specific prognostic impact of different mutation types compared with wild-type patients in future studies would aid in further defining the prognostic effect of mutated versus wild-type EGFR.

Confirmation of the benchmark of examined lymph node count in patients with node positive NSCLC using the SEER database

Wenhua Liang, Department of Thoracic Surgery/Oncology, The 1st Affiliated Hospital of Guangzhou Medical University, Guangzhou, China and colleague used the United States Surveillance, Epidemiology, and End Results (SEER) database from 1990 to 2010 regarding patients with stage I to IIIA completely resected non-small cell lung cancer (NSCLC) to determine its prognostic value among node positive patients. A benchmark for indicating sufficient lymph node examination among node negative NSCLC patients had been previously identified, using the SEER database and a Chinese multicentre registry (Liang et al. J Clin Oncol 2016). Professor Liang pointed out that the variability of lymph node examination in practice may result in some patients with less than 16 examined lymph nodes being under-staged and having a worse survival outcome. This benchmark agrees with the reported mean LN being harvested during complete pulmonary and mediastinal LN exploration, which could serve as a sign for adequate systematic lymph node sampling and theoretically be applicable to node positive patients as well.

In the study presented at ELCC 2017, SEER data were used and 12,407 patients were stratified according to the number of lymph nodes examined (<16 versus ≥16).

At a median follow up of 7.6 years (range: 0.1 to 10.0), examination of fewer than 16 lymph nodes emerged as a risk factor for poorer overall survival (OS) and cancer specific survival (CSS). By multivariate Cox regression, patients with <16 examined lymph nodes demonstrated increased risk of poorer OS, (hazard ratio [HR] 1.34; 95% confidence interval [CI] 1.27, 1.43; $p < 0.001$) and CSS (HR 1.36; 95% CI 1.27, 1.45) in comparison with patients having an examination of at least 16 lymph nodes. This analysis was done after adjusting for diagnostic year, sex, age, tumour size, differentiation, pathology and positive lymph node count and demonstrated results that remained consistent across different subgroups. Liang *et al.* Abstract 600

Practice point and future research opportunities

This study confirmed that 16 examined lymph nodes may be considered a benchmark for systematic lymph node examination among patients with node positive NSCLC, despite the number of positive lymph nodes. Node positive NSCLC with less than 16 lymph nodes being harvested for examination should be cautiously evaluated for the quality of lymph node examination and the indication for subsequent treatment.

LOCALLY ADVANCED NSCLC

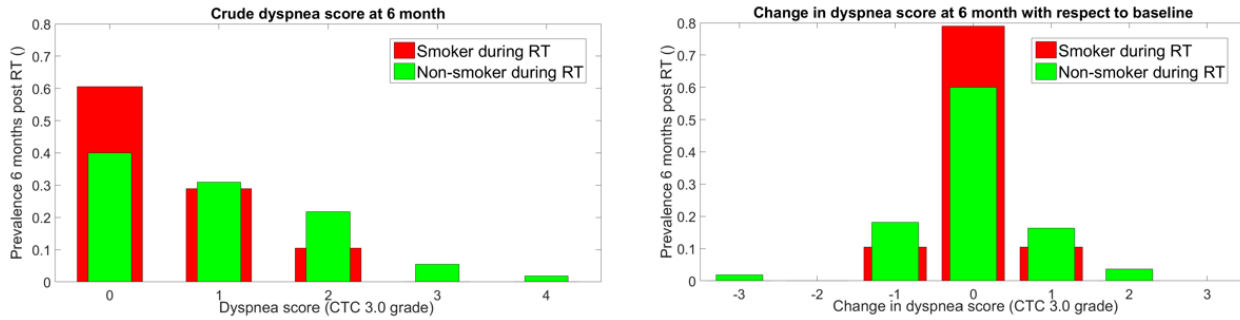
Patient data used for evaluation of radiation-induced lung toxicity prediction modelling in NSCLC

Gilles Defraene, Department of Oncology, KU Leuven - University of Leuven, in Leuven, Belgium, and colleagues used a dataset of patients with non-small cell lung cancer (NSCLC) who underwent radiotherapy to evaluate an outcome prediction model developed to identify patients at risk of dyspnea after radiotherapy. The model, published by Appelt *et al.* (*Acta Oncol* 2014), was identified in a literature search and is based on a review of radiation pneumonitis reports. The model retained the most important predictors for pneumonitis development contained in the reports: Mean lung dose (MLD) as dosimetric factor, and 6 other factors that influence the susceptibility of a patient to this condition, including pre-existing pulmonary comorbidity, age >63 years, mid/inferior tumour location, and sequential chemotherapy as risk factors; the model identified current smoking and smoking history as protective factors.

The team retrospectively assessed a dataset of 109 patients with NSCLC who received radiotherapy at the MAASTRO Clinic in 1.8 Gy fraction doses administered in two or more fractions per day up to 79.2 Gy. All treatments had been performed using 3D-conformal radiotherapy techniques to be consistent with the study that was the basis of the model. The required parameters were retrospectively collected together with the dyspnoea endpoint, according to common toxicity criteria (CTC) 3.0 scoring at baseline and at 6 months after radiotherapy.

Within 6 months after radiotherapy, 19.3% of patients had developed dyspnoea grade ≥ 2 per CTC scoring. Using logistic regression modelling on the dataset, current smoking and pulmonary comorbidity were confirmed as prognostic factors for dyspnoea, the odds ratios (OR) were 0.28 for current smoking ($p = 0.02$), and OR 2.95 for presence of a pulmonary co-morbidity ($p=0.02$). The OR for tumour location was outside of the reported 95% confidence interval (CI). The dosimetric factor in the published model, MLD, did not associate with outcome in any of the models employed in this study.

An evaluation of the change in dyspnoea with respect to the baseline score (delta dyspnoea ≥ 1) which had a prevalence of 18.6%, revealed that current smoking and pulmonary co-morbidity were no longer significant prognostic factors, OR 0.56 ($p = 0.27$) and OR 0.47 ($p = 0.21$), respectively.



Caption for image: Distribution of raw dyspnoea scores 6 months post radiotherapy (RT) with clearly lower scores in smokers (left). Changes in dyspnoea score from baseline (e.g. grade 2 at baseline which persists after RT is previously scored as grade 2 toxicity but now scored as grade 0 change) show similar normal distribution around zero, both for smokers and non-smokers (right). A ‘toxicity change’ approach could thus rule out a protective effect of smoking.

© Gilles Defraene

The explanation for this result that differs from the model is that both factors associated strongly with the baseline dyspnoea status. According to the authors, worse baseline dyspnoea is often a manifestation of existing comorbidities and may affect the probability of smoking cessation. The authors underscored that validated outcome prediction models with high discriminative power are important for cost-effective use of proton therapy for locally-advanced NSCLC, stressed the importance of including the consideration of delta toxicity, or change from baseline, in the development of meaningful prognostic models for radiotherapy outcome. Defraene *et al.* Abstract 74PD

Practice point and future research opportunities

This study used patient data to validate the utility of an outcome prediction model for the development of dyspnoea subsequent to radiotherapy, which revealed that the prognostic factors in the model did not adequately predict for delta toxicity endpoints. It is crucial to consider delta toxicity endpoints in prediction modeling in order to obtain meaningful models reflecting radiotherapy outcome.

ADVANCED NSCLC

Encouraging clinical benefit with atezolizumab in patients with advanced NSCLC with or without baseline brain metastases

Rimas V. Lukas, Department of Neurology and Section of Hematology & Oncology, University of Chicago, Chicago, USA presented findings from a safety analysis of pooled data from 1452 patients treated with atezolizumab for advanced non-small cell lung cancer (NSCLC) as second or subsequent line in the PCD4989g, BIRCH, FIR, POPLAR and OAK studies. Most patients had no brain metastases at baseline and 79 (5%) patients had previously treated stable/asymptomatic brain metastases.

The safety analysis demonstrated that the incidence of adverse events (AEs) and serious AEs (SAEs) was similar in patients with or without brain metastases: The incidence of an AE was 95% versus 92%, and the incidence of treatment-related AEs (TRAEs) was 70% versus 64% in patients with and without brain metastases, respectively. The most common treatment-related neurological AE was headache, which occurred in 8% of patients with and 3% of patients without brain metastases. Serious AEs (SAEs) were reported in 33% versus 36% and TRAEs were seen in 9% and 10% of the respective groups. Numerically higher rates of neurological AEs of 47% versus 30% and SAEs of 18% versus 9%, respectively, were reported in patients with versus those without brain metastases. No patients with brain metastases experienced a TRAE compared to 0.5% of patients without brain metastases.

An efficacy analysis was done on data from 850 patients with and without brain metastases participating in the OAK trial comparing atezolizumab and docetaxel. This analysis revealed an overall survival (OS) benefit favouring atezolizumab over docetaxel in patients with brain metastases: the median OS was 20.1 months in 38 patients receiving atezolizumab versus 11.9 month in 47 patients on docetaxel (hazard ratio [HR] 0.54; 95% confidence interval [CI] 0.31, 0.94). Median OS in patients without brain metastases was 13.0 months in 387 patients on atezolizumab versus 9.4 months in 378 patients on docetaxel (HR 0.75; 95% CI 0.63, 0.89).

The risk of developing new CNS lesions also appeared to be lower in patients with brain metastases at baseline with atezolizumab compared to docetaxel (HR 0.42; 95% CI 0.15, 1.18). NCT01375842, NCT02031458, NCT01846416, NCT01903993, NCT02008227. Lucas *et al.* Abstract 810

Practice point and future research opportunities

Approximately 20% to 40% of patients with advanced NSCLC develop brain metastases, which are associated with poorer survival. This study evaluated the safety of atezolizumab in patients with and without brain metastases at baseline. Atezolizumab demonstrated an acceptable safety profile and encouraging survival benefit in patients with NSCLC who had previously treated stable/asymptomatic brain metastases; similar safety profiles were observed in patients with and without brain metastases. An efficacy analysis of atezolizumab versus docetaxel in these

patients found an OS benefit with atezolizumab for both cohorts. These findings warrant further investigation of atezolizumab in patients with advanced NSCLC and CNS metastases.

Durable responses demonstrated with durvalumab in heavily pretreated patients with metastatic EGFR-mutated/ALK-positive NSCLC: ATLANTIC study results

Marina Garassino, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, and colleagues evaluated the clinical benefit of durvalumab, an engineered human IgG1 monoclonal antibody that blocks programmed death ligand-1 (PD-L1) binding to PD-1 and CD80, in the open-label single-arm phase II ATLANTIC study. The ATLANTIC enrolled 444 patients with stage IIIB/IV NSCLC who had undergone at least two previous systemic treatments, including one platinum-based chemotherapy regimen, and the cohort of 111 patients with epidermal growth factor receptor gene mutant/anaplastic lymphoma kinase-positive (EGFR-mutated/ALK-positive) disease (reported at ELCC 2017) had also received one tyrosine kinase inhibitor (TKI). All patients were treated with durvalumab at 10 mg/kg intravenously every 2 weeks for up to 12 months. The primary endpoint, objective response rate (ORR), was determined by independent central review and defined according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Secondary outcomes included the disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety (CTCAE v4.03).

Patients in the high PD-L1 ($\geq 25\%$ of tumour cells with membrane staining) cohort comprising 74 EGFR-mutated/ALK-positive patients, 64 patients with EGFR mutation, and 10 ALK-positive patients demonstrated a confirmed ORR of 12.2%, 14.1%, and 0%, respectively, compared to ORR of 3.6 across all molecular subgroups in 28 patients with low PD-L1 ($< 25\%$). The DCR was 20.3 months versus 7.1 months in the cohorts with high versus low PD-L1 expression, respectively.

No differences were seen in median PFS (1.9 months each) for 77 patients with high versus 30 patients with low PD-L1 expression. Median PFS was 2.0 versus 1.8 months in 66 patients with high PD-L1 and EGFR-mutated versus 12 patients with high PD-L1 plus ALK alteration, respectively. The median follow-up for OS was 6.5 versus 8.2 months for the cohorts with high versus low PD-L1 expression, respectively; comparisons of high versus low PD-L1 for median OS revealed non-significant differences of 13.3 versus 9.9 months, respectively, and 1-year OS was 54.8% versus 40.0% in the respective groups. Of patients with high PD-L1, those with EGFR mutation versus ALK alteration demonstrated median OS of 'not reached' versus 6.3 months, and 1-year OS rates of 57.4% versus 35.7%, respectively.

In responding patients, the median DoR was 7.4 months versus 'not calculated' due to small patient number for patients with high versus low PD-L1 expression.

Overall, the safety analysis did not differ from that of the EGFR/ALK wild-type cohort, wherein most adverse events (AEs) were low grade and immune-mediated. All AEs were managed according to standard treatment guidelines. Grade ≥ 3 treatment-related AEs (TRAEs) were

reported in 5.4% of patients and TRAEs leading to discontinuation occurred in 0.9% of patients. NCT02087423. Garassino *et al.* Abstract 82O

Practice point and future research opportunities

Clinical outcomes remain poor for patients with advanced or metastatic NSCLC who progress after 2 prior lines of treatment, making the need for novel third- or further-line therapies significant.

Although patients with EGFR-mutated/ALK-positive NSCLC have demonstrated some meaningful clinical responses to treatment with immune checkpoint inhibitors like durvalumab, efficacy in these patients versus efficacy in patients with EGFR/ALK wild-type NSCLC have been reported only in subgroup analyses, and data from phase III trials are needed to clarify the final role of durvalumab in locally advanced and advanced EGFR-mutated/ALK-positive NSCLC.

In ATLANTIC, durvalumab has demonstrated a manageable tolerability profile and provided durable responses in heavily pretreated patients with EGFR-mutated/ALK-positive locally advanced or metastatic NSCLC. Although the ORR was somewhat lower compared with the ORR reported for patients with EGFR/ALK wild-type, durable responses were still observed in heavily pre-treated patients with metastatic EGFR-mutated/ALK-positive NSCLC. Greater activity with durvalumab was also demonstrated for patients with high PD-L1 expression. However, these findings are limited by the short duration of follow-up and further confirmation is needed.

Durvalumab provides meaningful clinical benefit and durable responses in patients previously treated for stage IV squamous NSCLC

Vassiliki Papadimitrakopoulou, Thoracic/Head and Neck Medical Oncology, MD Anderson Cancer Center, Houston, USA, reported on a study that evolved from the Lung Master Protocol S1400, conducted by the National Clinical Trials Network group. The study began as a randomised phase II/III comparison of docetaxel and durvalumab in patients with stage IV squamous non-small cell lung cancer (NSCLC) and ECOG performance status 0-2. Due to the greater activity of durvalumab over docetaxel, the study was amended to a single-arm phase II trial of durvalumab. Eligible patients had stage IV, EGFR/ALK wild-type squamous NSCLC. Of these, 30 patients with a median age of 71.2 years were initially randomised to docetaxel and 68 patients with a median age of 66.0 years to durvalumab. The Zubrod performance status was 0/1/2 in 26%/62%/12% of patients, respectively; 92% of patients were current or former smokers, and all patients had received ≥ 1 prior systemic treatment regimen(s), including one platinum based.

The programmed cell death ligand-1 (PD-L1) status was known for 43 of the patients on durvalumab; 14 (32.6%) patients were classified as having high levels of PD-L1, defined as $\geq 25\%$ membrane staining, and 29 (67.4%) patients were classified as negative/low PD-L1 based upon 0%-24% of membrane staining.

The primary endpoint of overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors v1.1; for durvalumab it was 16.2% (95% confidence interval [CI] 7.4%, 24.9%), including one complete response (CR) and 10 partial responses (PR). The ORR for docetaxel was 6.7% (95% CI 0.0%, 15.6%). In responding patients, the median duration of response (DoR, a secondary endpoint) with durvalumab was 7.4 months (95% CI 4.4, 18.5 months).

The subanalysis according to PD-L1 expression status demonstrated an ORR of 14.3% (95% CI 0.0%, 32.6%) for patients with high levels of PD-L1 versus 6.9% (95% CI 0.0%, 16.1%) for patients with negative/low levels of PD-L1, the odds ratio (OR) for high versus negative/low was 2.25 ($p = 0.44$). However, no significant differences were seen for the comparison of high versus negative/low PD-L1 regarding median progression-free survival (2.3 months for both) or median overall survival (10.7 versus 11.0 months; hazard ratio, 0.85; $p = 0.67$).

The safety profile of durvalumab was consistent with previous reports. Treatment-related adverse events (TRAEs) were higher with docetaxel than with durvalumab; 100% versus 86.8%, respectively of docetaxel versus durvalumab treated patients experienced TRAEs and 73.3% of patients on docetaxel versus 33.8% of patients on durvalumab experienced grade ≥ 3 TRAEs. NCT02766335. Papadimitrakopoulou *et al.* Abstract 830

Practice point and future research opportunities

Durvalumab (MEDI4736), an engineered human IgG1 monoclonal antibody targeting PD-L1 demonstrated similar meaningful benefit as is seen with other anti-PD-1/PD-L1 antibodies in patients with advanced NSCLC. Durvalumab demonstrated clinical benefit and durable responses in a previously treated metastatic NSCLC population together with a manageable toxicity profile.

First-line atezolizumab monotherapy shows long term efficacy in PD-L1–selected patients with NSCLC: Update from the BIRCH trial

Solange Peters, HFR Fribourg-Hôpital Cantonal, Fribourg, Switzerland, presented an update of efficacy data from the phase II BIRCH trial of atezolizumab monotherapy (MPDL3280A) in PD-L1–selected patients with advanced non-small cell lung cancer (NSCLC). The patients had no prior chemotherapy and no active central nervous system metastases, and patients with EGFR mutation or ALK rearrangement were required to have had prior treatment with an appropriate tyrosine kinase inhibitor.

Atezolizumab is a humanised antibody targeting PD-L1 to inhibit the PD-1/PD-L1 interaction while preserving the PD-L2/PD-1 interaction, which potentially preserves peripheral immune homeostasis. Efficacy at 6 months was previously demonstrated in the BIRCH open-label, single-arm phase II study of atezolizumab at 1200 mg intravenously at 3-week intervals as first-line treatment or as subsequent second- or third-line treatment.

PD-L1 was centrally evaluated using the VENTANA SP142 IHC assay and all patients expressed PD-L1 on $\geq 5\%$ of tumour cells (TC) or tumour infiltrating cells (IC); 65 patients in a

high expression subgroup had PD-L1 expression on TC \geq 50% or IC \geq 10% (TC3 or IC3) and 138 patients in the overall population had PD-L1-expressing TC or IC \geq 5% (TC2/3 or IC2/3). The primary objective of BIRCH was the efficacy of atezolizumab by objective response rate (ORR) according to independent review facility (IRF) per RECIST v1.1 and key secondary endpoints included duration of response (DoR), progression-free survival (PFS) by IRF and investigator, ORR by investigator, overall survival (OS), and safety.

Overall, the activity of atezolizumab correlated with the extent of PD-L1 expression on TC and IC, with the highest activity seen in patients demonstrating expression on both cell types. At a median follow-up of 22.5 months, the investigator-assessed ORR was 25% in all treated patients (TC2/3 or IC2/3), and median DoR in the responding patients was 16.5 months, (95% confidence interval [CI] 9.9, not estimable [NE]). The 12-month OS rate was 66.4%, and median OS was 23.5 months. The median 12-month PFS rate was 66.4% and median PFS was 7.3 months.

In the high expression subgroup (TC3 or IC3) the ORR was 34% and median DoR in the responding patients was NE (95% CI 8.5, NE). The 12-month OS rate was 66.4%, and median OS was 26.9 months. The 12-month PFS rate was 61.5% and median PFS was 7.3 months.

Responses were observed in patients with both EGFR and KRAS mutant and wild-type tumours. Overall, the ORR was 31% in patients with EGFR mutant tumours compared to ORR of 22% in patients with EGFR wild-type. In the high PD-L1 expression cohort, the ORR was 25% and 31% in patients with EGFR mutant and wild-type tumours, respectively.

Comparison of the high and low PD-L1 expression cohorts revealed the ORR was 31% and 22% in patients with KRAS mutant and wild-type tumours, respectively, in the overall cohort versus ORR of 38% and 30% in patients with KRAS mutant and wild-type tumours, respectively.

The safety profile was consistent with that previously reported in BIRCH and with previous atezolizumab NSCLC trials. NCT02031458. Peters *et al.* Abstract 840

Practice point and future research opportunities

With a median follow-up of 22.5 months, patients with advanced NSCLC receiving atezolizumab continued to demonstrate durable clinical benefit in the BIRCH study. Atezolizumab was active in patients with both EGFR and KRAS mutant and wild-type tumours. These results support ongoing phase III trials evaluating atezolizumab compared to chemotherapy as first line therapy. Higher PD-L1 expression correlated with higher ORR and may allow identification of patients most likely to benefit from atezolizumab.

Symptom amelioration with osimertinib according to patient reported outcomes in advanced NSCLC

Chee Khoon Lee, Clinical Research Unit of Cancer Services, St. George Hospital, Kogarah, Australia, reported quality of life data from the phase III AURA3 trial that showed improved symptom control with osimertinib in patients with advanced epidermal growth factor receptor

(EGFR) mutated non-small-cell lung cancer (NSCLC) who had progressed after first-line EGFR-tyrosine kinase inhibitor (TKI) therapy. In AURA3, 419 patients were randomised 2:1 to receive 80 mg of oral osimertinib daily or standard chemotherapy. The trial demonstrated significantly longer progression-free survival (PFS) of 10.1 months with osimertinib versus 4.4 months with chemotherapy (hazard ratio [HR] 0.30; 95% confidence interval [CI] 0.23, 0.41; $p < 0.001$).

Patient-reported outcomes (PROs) of clinically relevant symptoms were a secondary endpoint of AURA3. At baseline and at regular intervals up to, and beyond disease progression, patients completed two European Organisation for Research and Treatment of Cancer (EORTC) questionnaires, the lung cancer specific QLQ-LC13 and the QLQ-C30, which assess general cancer symptoms. Baseline PROs showed no statistical differences between the 230 patients on osimertinib and the 116 patients on chemotherapy; mean baseline scores (scale: 1 to 100) of the main criteria in patients overall were cough, 32.8; chest pain, 17.1; dyspnoea, 24.1; fatigue, 32.5; and appetite loss, 23.3. Deterioration or improvement was defined as an increase or decrease, respectively, of ≥ 10 points from baseline.

Patient-reported symptom improvement rates for the comparison of osimertinib to chemotherapy for cough, chest pain, dyspnoea, fatigue, and appetite loss were 1.51 ($p = 0.144$), 1.66 ($p = 0.149$), 2.71 ($p < 0.001$), 1.96 ($p = 0.008$), and 2.50 ($p = 0.006$), respectively. Patient reports also indicated that the time to deterioration of key symptoms was longer with osimertinib versus chemotherapy: for cough, the median time to deterioration was 8.3 versus 6.1 months (HR 0.74; $p = 0.90$); chest pain was 12.4 versus 2.1 months (HR 0.52; $p < 0.001$); dyspnoea was 6.1 versus 0.6 months (HR 0.42; $p < 0.001$); fatigue was 5.6 versus 2.7 (HR 0.66; $p = 0.011$), and appetite loss was 15.0 versus 4.3 months (HR 0.46; $p < 0.001$).

Osimertinib significantly improved global health status ($p = 0.007$), physical functioning ($p = 0.002$), role functioning ($p < 0.001$), and social functioning ($p < 0.001$) scores compared to chemotherapy. There was a non-statistically significant trend towards improved emotional and cognitive function with osimertinib. These data had a potential confounding effect due to crossover at 24 weeks by more than one-third of chemotherapy patients to osimertinib. NCT02151981. Lee *et al.* Abstract 85O

Practice point and future research opportunities

The changes in patient-reported symptoms demonstrated in the AURA3 trial support improved patient outcome for osimertinib over chemotherapy in patients with advanced NSCLC; in addition, the time to deterioration of key symptoms was longer and more patients also demonstrated improvement in global health status with osimertinib over chemotherapy. To be able to reduce cancer symptoms and improve quality of life in addition to PFS in these patients is a major achievement.

Osimertinib is a next-generation EGFR-TKI approved for patients with EGFR T790M mutation-positive metastatic NSCLC; these patients should now receive frontline TKI (first or second generation) and second-line osimertinib when they have a T790M resistance mutation, rather

than switching to chemotherapy. Options other than chemotherapy for the subsequent third line of therapy require investigation.

It must be kept in mind that osimertinib is effective in 55% of patients with NSCLC and EGFR whose TKI resistance to frontline TKI is due to a T790M gatekeeper mutation; therefore, more research is needed to find better second-line treatments for patients with a different mechanism of resistance, for whom chemotherapy is currently the only option. The opportunity for an indication for frontline osimertinib in all EGFR mutated NSCLC is being evaluated in the FLAURA trial that is comparing a first generation TKI to osimertinib.

Ensartinib demonstrates clinical benefit in patients with ALK-positive NSCLC and CNS metastases

Karen L. Reckamp, Medical Oncologist, City of Hope, Duarte, USA explained that Ensartinib (X-396) is a potent small molecule tyrosine kinase inhibitor (TKI) that has activity against ALK but also targets MET, ABL, Axl, EPHA2, LTK, ROS1 and SLK. Animal studies have shown that the CNS concentration of ensartinib was 4 times higher than the IC50 for growth inhibition of ALK-positive cells in vitro when ensartinib was administered to mice at the therapeutic dose. Ensartinib was significantly more effective than crizotinib at inhibiting the intracranial growth of the SH-SY5Y neuroblastoma model, which harbours the F1174L mutation, prompting investigators to conduct this multicentre phase I/II study.

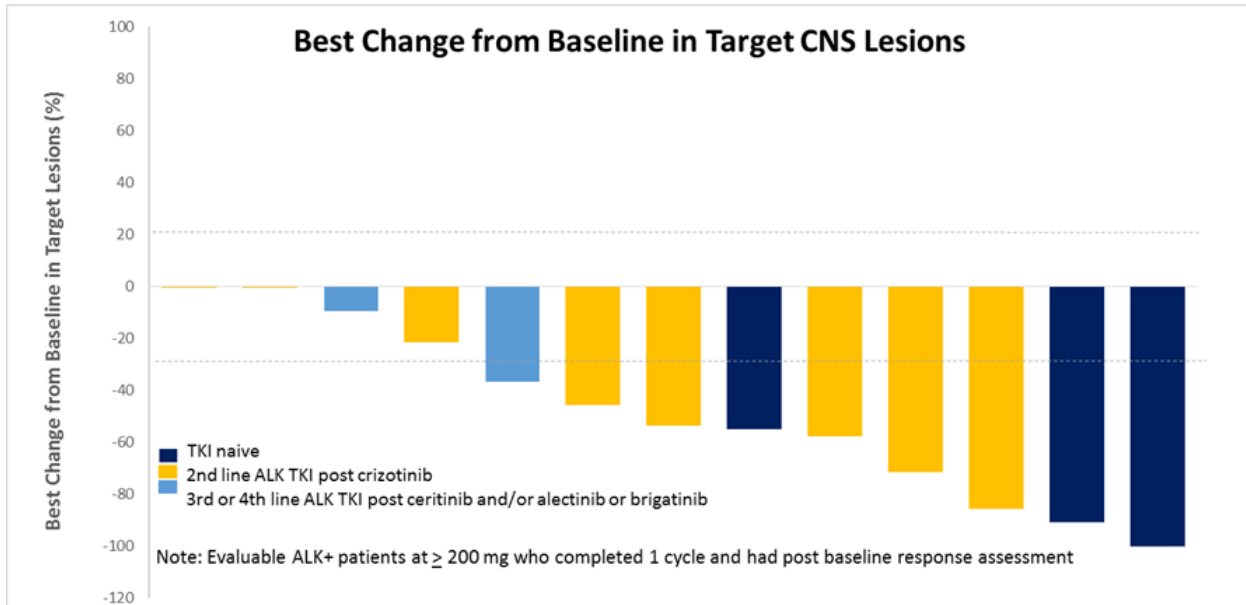
The study enrolled patients with stage IIIB/IV ALK-positive non-small cell lung cancer (NSCLC); patients with asymptomatic central nervous system (CNS) metastases, both with or without systemic disease were eligible for enrolment but patients with only CNS disease were required to have at least 1 measurable target lesion ≥ 3 mm in diameter. ALK TKI naive patients and also patients that had received prior crizotinib or a 2nd generation ALK TKI were included in this trial. The general cohort comprised 62 patients with a mean age of 55 years and were 53% female with measurable systemic disease; the CNS metastases cohort contained 30 patients with a mean age of 55 years and 60% were female plus with ≥ 1 measurable target lesion of ≥ 3 mm diameter. In the CNS metastases cohort, 53% of patients had target lesions that could be evaluated.

All patients received oral ensartinib at 225 mg daily, with or without food, on a continuous 28-day schedule. The efficacy measure was objective response rate (ORR) according to RECIST v1.1 and CNS response was assessed by modified Response Assessment in Neuro-Oncology Criteria (RANO).

CNS responses were observed in all patients, whether they were ALK TKI naive or had received prior treatment with either crizotinib or a 2nd generation ALK TKI. Although no complete response was observed in the general cohort, the ORR was 63% and the disease control rate (DCR) was 82%.

In the CNS metastases cohort, the ORR was 40%, and included 10% of patients achieving complete responses; the DCR was 87%. Of the 16 patients demonstrating the best intracranial

target lesion response, the ORR was 69% and the DCR was 94%. Among the patients with baseline lesions, 3 were ALK TKI naive; the intracranial RR in these patients was 100%. Of 8 patients with target lesions receiving prior crizotinib, the intracranial RR was 62% and 2 patients receiving a prior 2nd generation ALK TKI achieved one PR and one SD.



© Karen L. Reckamp.

The median duration of response among the responding patients was 5.8+ months. The longest duration of intracranial response was 24 months. Approximately a third of the patients in the CNS metastases cohort remained on treatment for >1 year, including those receiving ≥ 3 prior lines of therapy. The safety analysis, the primary endpoint of this study, showed that the most common adverse events at grade 3 across both cohorts were rash in 11% of patients, and pruritis in 4% of patients. NCT02767804 and NCT01625234. Reckamp *et al.* Abstract 880

Practice point and future research opportunities

These clinical findings support the preclinical results, which indicated that the use of ensartinib may result in favourable therapeutic outcomes in patients with ALK-positive NSCLC and CNS metastases. Ensartinib was beneficial in ALK-positive patients and in patients heavily pre-treated with other TKIs. A CNS response was observed in all treated patients.

Ensartinib is being investigated in the ongoing phase III eXalt3 trial, which is evaluating the CNS response rate and time to CNS progression with ensartinib compared with crizotinib in the first-line setting for patients with ALK-positive NSCLC.

Patients with NSCLC that have been pre-exposed to PD-1/PD-L1 inhibitors demonstrate greater response to salvage chemotherapy

Sacha I. Rothschild, Department of Medicine, Division of Oncology, University Hospital Basel, in Basel, Switzerland presented preliminary findings that could potentially change the sequence of cancer treatment delivery. Professor Rothschild's team conducted a retrospective analysis of data from 82 patients with stage IV non-small cell lung cancer (NSCLC), including 63 with adenocarcinoma, 18 with squamous cell carcinoma, and one case of large cell carcinoma. Of these, 56 patients had received prior treatment with nivolumab, 7 had received pembrolizumab, and 4 patients had received atezolizumab. The remaining 15 patients had not received PD-1/PD-L1 inhibitors and served as controls. Patients in the immunotherapy cohort had also been pre-treated with a mean of 2.37 prior chemotherapy regimens and the controls received 1.93 prior regimens. Salvage chemotherapy included docetaxel in 62% of patients, pemetrexed in 20%, paclitaxel in 6%, and 12% of patients received other agents.

Computed tomography scans performed within the first month of the study and every 6 weeks thereafter showed a significantly higher partial response rate of 27% in patients receiving prior immunotherapy compared to 7% for controls (odds ratio 0.3, $p < 0.0001$). Stable disease was achieved by 51% versus 53%, and progressive disease was experienced by 22% versus 40% of patients receiving prior immunotherapy versus controls, respectively.

Neither age, gender, the number of prior chemotherapy regimens, tumour histology, smoking status, nor different salvage chemotherapy regimens independently associated with the likelihood of achieving partial response according to multiple logistic regression. Rothschild *et al.* Abstract 91PD

Practice point and future research opportunities

Immune checkpoint inhibitors targeting PD-1/PD-L1 are active for patients with stage IV NSCLC who have progressed after platinum-based chemotherapy. However, the need remains to better define patient responses to salvage chemotherapy in terms of their previous exposure to these checkpoint inhibitors. This is the first study to formally describe greater response to salvage chemotherapy in patients previously receiving immunotherapy.

In this study, the odds of achieving a partial response to salvage chemotherapy were significantly higher in patients having prior exposure to PD-1/PD-L1 inhibitors.

These preliminary results suggest that immunotherapy can change the natural history of the disease and the micro-environment of the tumour, therefore rendering it more sensitive to chemotherapy. This could potentially point to new areas of research and new sequences of treatment.

This observed difference however warrants confirmation in larger cohorts. Ongoing investigations include the duration of response as well as evaluation of toxicity.

Prospective study shows the cobas[®] test can detect EGFR mutation in plasma ctDNA with good concordance between ctDNA and tumour samples

Rajiv Kumar, Lung Cancer Department, The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, London, UK explained that the cobas[®] test is currently used in clinical practice on tumour tissue and has been approved for ctDNA EGFR testing from plasma samples, but the diagnostic performance of the test had not yet been established. His team conducted this prospective study using data from patients diagnosed with advanced non-small cell lung cancer (NSCLC) at the Royal Marsden Hospital between November 2015 and November 2016 to evaluate the diagnostic performance of the cobas[®] platform on ctDNA in plasma samples. To be included in the dataset, patients were required to have an available tissue EGFR result. Peripheral blood samples were collected in cell-free DNA detection (cfD) tubes and analysed using the cobas[®] platform per manufacturer's instructions.

The median age of patients in the study was 68 years. Adenocarcinoma was diagnosed in 89% of patients, poorly differentiated carcinoma in 4%, squamous cell carcinoma in 3%, adenosquamous in 2.5%, and other lung cancer histology was diagnosed in 1.5% of patients. The smoking status was never-smoker in 30% of patients, while 58% were ex-smokers, 10% were current smokers, and 2% of patients had an unknown smoking history. Stage IV disease was reported in 93% of patients, and stage III disease was seen in 7% of patients. Thoracic-only disease was observed in 42% of patients.

The tissue EGFR analysis had been performed on the cobas[®] platform in the majority (79%) of patients, while EGFR analysis had been done using Illumina next generation sequencing (NGS) in 7.5%, and Therascreen[™] in 1% of patients. Tumour tissue was not available for 10% of patients. All plasma samples were tested on the cobas[®] platform.

There was good agreement between ctDNA and the tumour regarding the presence of EGFR mutation. The concordance rate between ctDNA and the tumour was 87%, with sensitivity of 65%, and specificity of 98%. The positive predictive value was 95%, and the negative predictive value was 85%.

The concordance rate between tumour and ctDNA in patients with an EGFR mutation was 55% for thoracic-only disease and 75% for extra-thoracic disease.

The mean time to EGFR result was shorter for ctDNA samples, at 8.4 days, than for tumour tissue, which took 11.2 days ($p = 0.07$).

The failure rate for ctDNA samples was just 2.4%.

CONCORDANCE IN THORACIC VS EXTRATHORACIC DISEASE

Concordance in patients with thoracic ONLY disease

	Tissue <i>EGFR</i> Mutant	Tissue <i>EGFR</i> wildtype	TOTAL
Plasma <i>EGFR</i> mutant	15 (21%)	0	15 (21%)
Plasma <i>EGFR</i> wildtype	12 (17%)	44 (62%)	56 (79%)
TOTAL	27 (38%)	44 (62%)	71 (100%)

(Percentages calculated as a proportion of total sample number (i.e. 71))

Plasma *EGFR* mutant concordance rate
55%

Concordance in patients with extrathoracic disease

	Tissue <i>EGFR</i> Mutant	Tissue <i>EGFR</i> wildtype	TOTAL
Plasma <i>EGFR</i> mutant	21 (22%)	2 (2%)	23 (24%)
Plasma <i>EGFR</i> wildtype	7 (7%)	64 (68%)	71 (76%)
TOTAL	28 (30%)	66 (70%)	94 (100%)

(Percentages calculated as a proportion of total sample number (i.e. 94))

Plasma *EGFR* mutant concordance rate
75%

Caption for image: Concordance rate between tumour and ctDNA in patients with an *EGFR* mutation in thoracic vs extrathoracic disease.

© Rajiv Kumar

EGFR mutations in Exon 19 and T790M were detected only in plasma ctDNA due to tissue failures involving 2 samples.

Mutation frequency and concordance in diagnostic cohort

Tissue EGFR mutation	Frequency of EGFR mutation (n (%))
Exon 19 deletion	18 (48.7%)
L858R	14 (37.8%)
S768I	2 (5.4%)
Exon 20 insertion	1 (2.7%)
L861Q	1 (2.7%)
T790M	1 (2.7%)

		Plasma EGFR Result					
		Exon 19 Deletion	L858R	L861Q	L858R S768I	T790M	Wildtype ¶
Tissue EGFR Result	Exon 19 deletion	13 (35.1%)					5 (13.5%)
	Exon 20 insertion						1 (2.7%)
	L858R		9 (24.3%)				5 (13.5%)
	L861Q			1 (2.7%)			
	S768I				1 (2.7%)		1 (2.7%)
	T790M					1 (2.7%)	

(Percentages calculated as a proportion of total sample number (i.e. 37))

© Rajiv Kumar

Mutation frequency and concordance in acquired resistance cohort

Tissue EGFR mutation	Frequency of EGFR mutation (n (%))
Exon 19 deletion	8 (44%)
Exon 19 deletion & T790M	4 (22%)
L858R	4 (22%)
Exon 20 insertion	1 (5.6%)
T790M	1 (5.6%)

		Plasma EGFR Result			
		Exon 19 Deletion	Exon 19 Del & T790M	L858R	Wildtype ¶
Tissue EGFR Result	Exon 19 deletion	5 (27.8%)			3 (16.7%)
	Exon 19 Del & T790M		3 (16.7%)		1 (5.6%)
	L858R			2 (11.1%)	2 (11.1%)
	Exon 20 insertion				1 (5.6%)
	T790M		1 (5.6%)		

(Percentages calculated as a proportion of total sample number (i.e. 18))

© Rajiv Kumar

This study confirmed that the cobas[®] test on ctDNA may be used for diagnosis of an EGFR

mutation in advanced NSCLC with excellent specificity and moderate sensitivity. The authors recommended that the cobas[®] test for ctDNA be incorporated into clinical practice to triage patient care. Kumar *et al.* Abstract 95PD

Practice point and future research opportunities

This prospective study provides evidence that detection of EGFR mutations in circulating tumour DNA from plasma samples can be accomplished using the cobas[®] platform. Assays of ctDNA offer a non-invasive method of finding EGFR mutations that can guide the clinical decision to offer EGFR inhibitor treatment to patients with NSCLC. In this study, EGFR mutations were detected in ctDNA with excellent specificity and the turnaround time quicker with ctDNA samples. Further confirmation of these findings is needed before this method can enter the routine diagnostic setting.

Brigatinib demonstrates greater than 50% confirmed response in patients with crizotinib-refractory ALK-positive NSCLC: Updates from the ALTA trial

Maximillian J. Hochmair presented an update from the pivotal phase II ALTA trial of the investigational next-generation anaplastic lymphoma kinase (ALK) inhibitor, brigatinib, in patients with ALK-positive non-small cell lung cancer (NSCLC). The ongoing, two-arm, open-label, multicentre trial enrolled 222 patients with locally advanced or metastatic ALK-positive NSCLC who had progressed on crizotinib. The ALTA evaluated brigatinib at 2 dose levels based on a previous trial demonstrating that tumour responses and adverse events (AEs) varied with the starting dose; 112 patients were randomised to 90 mg of brigatinib once daily and 110 patients to 180 mg once daily following a 7-day lead-in of 90 mg once daily. The major efficacy outcome measure was confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included investigator-assessed ORR, duration of response (DoR), intracranial ORR, and intracranial DoR.

At a median follow-up of 8 months (range 0.1 to 20.2 months) 53% of the patients receiving the recommended dosing regimen (90→180 mg), achieved a confirmed overall response (OR) as assessed by IRC and 54% of these patients showed OR as assessed by investigator. Among responding patients, the median DoR was 13.8 months, as assessed by IRC and 11.1 months by investigator assessment. Patients receiving brigatinib at the lower dose demonstrated a confirmed OR of 48% by IRC and 45% by investigators assessment. Median progression-free survival (PFS) was 15.6 months at the recommended dose and 9.2 months at the lower dose.

Additionally, 18 (67%) of patients with measurable brain metastases achieved a confirmed intracranial OR by IRC assessment. Of the patients showing an intracranial response, 78% of patients in the 90 mg arm and 68% of patients in the 90→180 mg group maintained a response for at least 4 months.

The most common adverse events (AEs), occurring ≥25% of patients, with brigatinib were nausea, diarrhoea, fatigue, cough, and headache. Treatment-emergent AEs (TEAEs) at the low

versus recommended dose included nausea in 33% versus 40% of patients, diarrhoea in 19% versus 38%, headache in 28% versus 27%, and cough in 18% versus 34% patients, respectively. Grade ≥ 3 events occurring with $\geq 3\%$ frequency in the respective dose levels were hypertension in 6% versus 6%, increased blood creatine phosphokinase in 3% versus 9%, pneumonia 3% versus 5%, and increased lipase in 4% versus 3% of patients. Pulmonary AEs with early onset (median onset on day 2) occurred in 14 (6%) treated patients; of these, 3% were grade ≥ 3 . These events did not occur after escalation to 180 mg in arm B, and 7 were successfully retreated. NCT02094573. Hochmair *et al.* Abstract 97P

Practice point and future research opportunities

These updated ALTA trial data revealed that brigatinib showed substantial efficacy plus an acceptable safety profile at 2 dose levels. Patients receiving the recommended 180 mg with 90 mg lead-in showed an improvement in efficacy endpoints, particularly PFS, with no increase in early pulmonary AEs, compared with 90 mg.

On April 28, 2017, brigatinib was granted Accelerated Approval from the US Food and Drug Administration for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. This indication is approved under Accelerated Approval based on the tumour response rate and duration of response demonstrated in the ALTA trial. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. The efficacy and safety of brigatinib is also being evaluated compared to crizotinib in patients with locally advanced or metastatic ALK-positive lung cancer in the phase III ALTA 1L trial.

The development of brain metastases in molecular selected and wild-type patients with NSCLC included in clinical trials

Susana Cedrés and colleagues at Vall d'Hebron University Hospital/Vall d'Hebron Institute Oncology, in Barcelona, Spain investigated the characteristics and development of brain metastases according to the molecular profile of patients with advanced non-small cell lung cancer (NSCLC). Their analysis included patients with EGFR, KRAS, HER2 mutations and ALK, ROS1 and RET rearrangements that participated in clinical trials between 2009 and 2015 at their centre as compared a cohort of patients with wild type adenocarcinoma. Of the 200 patients in the analysis, 76 had wild type, 45 had mutated EGFR, 51 had ALK rearrangement, 21 had KRAS mutation, 3 had ROS1 rearrangement, 2 had HER2 mutation and 2 patients had rearranged RET. The patients' median age was 57 years (range: 26 to 82 years), 52% were male, and 59% were smokers. The performance status (PS) was 1 in 60% of patients, 98% of patients were stage IV, and 92% of patients had adenocarcinoma. The first treatment administered was with a selective inhibitor in 73% of EGFR-mutated and 58% of ALK-positive patients.

At a median follow-up of 23 months (95% confidence interval [CI] 1.6, 104.6) the overall survival (OS) as estimated by the Kaplan Meier method was 33 months for all patients versus 57 months for patients with EGFR mutation versus 40 months in patient with ALK-positive disease versus 31 months in patients with KRAS mutation versus 19 months in patients with wild-type tumours.

Significant differences in OS were observed for the molecular selected population versus wild-type, women versus men, PS 0/1 versus PS2 and in smokers versus non-smokers. The OS was 55 months in the molecularly selected population compared to 19 months in wild-type patients ($p < 0.001$) and OS was 55 months in women compared to 23 months in men ($p = 0.002$). The OS was 21 versus 7 months in patients with PS 0/1 versus PS2 ($p < 0.001$) and 51 months versus 23 months in smokers versus non-smokers ($p = 0.002$).

Brain metastases were detected in 86 patients, including 36 ALK, 25 wild-type, 14 EGFR, 8 KRAS, 2 ROS, and 1 RET; of these patients, 87% received local therapy. Brain metastases were more common in women, non-smokers, and patients with ALK (all comparisons $p < 0.001$).

The median time from diagnosis of NSCLC to the development of brain metastases in the entire population was 6 months; brain metastases were detected at a median of 6 months in molecular selected patients and at a median 5 months in wild-type patients ($p = 0.44$). The median OS after development of brain metastases was 14 months (28 months in patients with EGFR-mutated, 26 months for ALK-positive, and 8 months for wild-type patients ($p < 0.001$)). No differences in OS were detected between patients with or without brain metastases ($p > 0.05$). Independently of the target agent, no significant differences in OS were found in patients with brain metastases who received local therapy versus systemic treatment ($p > 0.005$). Patients receiving EGFR or ALK inhibitors after diagnosis of brain metastases demonstrated greater benefit than patients who began treatment before the diagnosis of brain metastases of 86 months versus 57 months for EGFR inhibitors and 55 months versus 35 months for ALK inhibitors, respectively (both comparisons $p > 0.05$). Cedrés *et al.* Abstract 106P

Practice point and future research opportunities

Molecular selection identifies several oncogenic drivers that can be targeted with selective inhibitors. In this analysis, molecular selected patients with NSCLC who received targeted agents demonstrated prolonged survival. The brain is a frequent site of disease progression and metastasis, but the prognosis of these patients is independent of the local therapies administered.

Cancer patients on immunotherapy may be a greater risk of complications from influenza vaccine

Sacha I. Rothschild, Department of Medicine, Medical Oncology, University Hospital Basel in Basel and colleagues throughout Switzerland conducted the first study to evaluate whether immunization against influenza might trigger an exaggerated immune response in patients receiving PD-1/PD-L1 checkpoint inhibitors. The investigators conducted this prospective study in 23 patients with a mean age 58.7 years; 16 patients had non-small-cell lung cancer (NSCLC), 4 patients had renal cell carcinoma (RCC), and 3 patients had melanoma. Slightly more than half of the patients had received at least two previous lines of chemotherapy and 22 patients were currently receiving nivolumab, and one patient was on pembrolizumab. All patients were vaccinated with a trivalent influenza vaccination between October and November 2015 and followed for safety, efficacy, and the frequency of immune-related adverse events (irAEs). A

control group of 10 health individuals who were age-matched to the patients also received the same vaccine and served as control.

All patients showed an adequate immune response to the vaccine and developed antibody titres against all 3 viral strains. No vaccination-related severe adverse events were noted in the first 30 days following vaccination. The rates of grade 1 local irritation at the injection site in the deltoid muscle were similar between patients and controls. None of the vaccinated participants was diagnosed with influenza infection during the 2015/2016 influenza season.

However, an unusually high frequency of irAEs was observed in the vaccinated patient cohort; 52.2% of patients experienced an irAE, with 6 (26.1%) patients experiencing severe grade 3 or 4 irAEs. The frequency of irAEs was higher compared to the expected rate of 25.5% observed in unvaccinated patients treated with PD-1/PD-L1 inhibitors at the Basel centre (9.8% for grade 3 or 4 events), and the rate of 30-35% that has been reported in the literature.

The most commonly reported immune-related adverse events were skin rashes and arthritis (13% each), followed by colitis and encephalitis (8.7% each), hypothyroidism, pneumonitis and neuropathy (4.3% each). The investigators evaluated whether PD-1 blockade may increase the immune response, and induce an inflammatory syndrome by measuring the levels of inflammatory chemokines in the patients' peripheral blood but found no significant change in inflammatory chemokine levels in either patients or controls during the early phase after vaccination.

Based on these observations, the authors currently advise a case-by-case decision regarding seasonal influenza vaccination for patients undergoing single-agent PD-1 or PD-L1 blockade, particularly those with lung cancer until results from larger cohorts are available. Rothschild *et al.* Abstract 112P

Practice point and future research opportunities

Use of immune checkpoint inhibitors is now standard clinical practice for many oncology patients, and these patients, especially those with lung cancer, also face increased risk for complications from influenza. Although routine influenza vaccination has long been recommended for cancer patients, this study raises the warning that long-term immune-related events following vaccination may be higher in patients receiving immunotherapy, despite a good serological protection and no short-term toxicity. This study is important as it is the first to investigate the impact of influenza vaccination in patients receiving immunotherapy for cancer and the findings suggest that they may be at increased risk for serious toxicities including encephalitis.

This report of an increased rate of immunological toxicity is concerning and should be studied in a larger patient population. Data from a larger cohort, preferably in a controlled prospective study, is needed to formulate a recommendation for or against vaccination in patients receiving PD1/PD-L1 inhibitors.

Expanded RNA and protein-based testing detects actionable biomarkers in driverless lung carcinoma

Zoran Gatalica, Caris Life Sciences, Phoenix, USA, pointed out that, while, massively parallel-gene next generation sequencing (NGS) has improved the detection of targetable mutations in non-small cell lung cancer (NSCLC), there remain many NSCLC cases that have no druggable target or conventional lung cancer pathogenic mutation (“driverless” cancer). Driverless NSCLC does not contain ROS1, ALK or cMET alterations that may be identified by extensive DNA sequencing and targeted in-situ hybridizations (ISH). Therefore, to identify putative targets, the investigators performed expanded platform testing, both RNA and protein-based.

The NGS was done on 522 NSCLC cases in the Caris Life Sciences database using a 592 gene sequencing panel, (Agilent SureSelectXT; Illumina NextSeq) and ISH that identified 21 patients with driverless tumours. Expanded analysis included an RNA-based fusion panel comprised of 52 genes (Archer FusionPlex) and protein-expression for EGFR, TS and PD-L1 by immunohistochemistry (IHC).

Targetable NTRK gene fusions, such as NTRK3:ETV6 and NTRK1:TPM3 were detected in two cases and c-MET exon 14 skipping in one case by expanded platform profiling. The IHC identified PD-L1 expression in 7 (3 low and 4 high TPS) cases, EGFR over-expression (H-score>200) in 7 cases, and TS under expression in 13 cases. Two low allele frequency pathogenic mutations (PIK3CA and GNAS), and 3 gene amplifications (MDM2, CDK4 and CDKN2A) were identified using the initial NGS panel as potential non-characteristic drivers in 4 cases.

The authors commented that the routine use of NGS leaves a small proportion (4.2%) of cases without a standard biomarker-guided therapy recommendation. These cases are characterised by a lower total mutational load (TML), 5.2/Mb, than reported for NSCLC (for example, TCGA mean: 8.9/Mb). The TML range in this series was 1-10/Mb (mean 5.2/Mb). Gatalica *et al.* Abstract 124P

Practice point and future research opportunities

This analysis demonstrated that expanded multiplatform testing (RNA- and protein-based) could be used to find targets in addition to those identified by NGS. This expanded testing detected biomarkers for immune checkpoint inhibitors that could be used in 33% of patients, and NTRK and c-Met targeted therapies could be used in 23% of cases. Over-expression of EGFR was detected in 57% of cases and under expression of TS was identified in 72% of cases that could also provide additional information for therapy guidance in specific cancer types.

METASTASES TO AND FROM THE LUNG

The molecular status of the tumour associates with the anatomic sites of metastases at diagnosis of NSCLC

Chantal Kuijpers, Department of Pathology, University Medical Centre Utrecht in Utrecht, Netherlands, and colleagues used the Netherlands Cancer Registry for the year 2013 to define a cohort of patients with stage IV non-squamous non-small cell lung cancer (ns-NSCLC). The team looked for targetable molecular alterations, including EGFR mutations, KRAS mutations, or ALK translocation to determine which anatomic sites of metastasis could be associated with specific mutations prior to treatment. Tumours were matched to the Dutch Pathology Registry (PALGA), and data on molecular testing for the targeted mutations were extracted.

The cohort comprised 2884 patients with stage IV ns-NSCLC, of whom 220 (7.6%) patients were EGFR-mutated, 775 (26.9%) were KRAS-mutated, 42 (1.5%) were ALK-positive, and 1117 (38.7%) patients had none of these 3 mutations (triple-negative tumours). The most frequent sites of metastasis were bone (33.7%), lung (23.6%), pleura (23.4%), and brain (22.5%).

Adjusted odds ratios (OR) by multivariable logistic regression analyses revealed that 41.1% of patients with EGFR-mutated tumours had bone metastases at diagnosis, which was more frequent than patients with KRAS mutations (OR 2.01; 95% confidence interval [CI] 1.48, 2.72), ALK-positive (OR 2.22; 95% CI 1.09, 4.50), and triple-negative tumours, (OR 2.09, 95% CI 1.56-2.81).

The sites of metastasis were also associated with the mutations; using triple-negative tumours as the comparator, EGFR-mutated tumours more often metastasized to the pleura (OR 1.50; 95% CI 1.08, 2.08) and liver (OR 1.52; 95% CI 1.00, 2.25), and less often to the brain (OR 0.67; 95% CI 0.45, 0.99) or adrenal gland (OR 0.49; 95% CI 0.31, 0.79). Compared to triple-negative tumours, KRAS-mutated and ALK-positive tumours more often metastasised to the lung (OR 1.35; 95% CI 1.09, 1.68) and liver (OR 2.09; 95% CI 1.00, 4.35). Kuijpers *et al.* Abstract 1470

Practice point and future research opportunities

This analysis showed that the patterns of metastasis may differ according to the mutations and molecular status of the tumour in NSCLC. These findings suggest that the sites of metastasis differed according to the genetic driver of the tumour. Since EGFR-mutated patients often have a better prognosis, it may be of clinical benefit to screen for and treat skeletal-related events in patients with NSCLC and an EGFR mutation.

EGFR-mutation testing by ctDNA in plasma is more sensitive in patients with extrathoracic disease

According to Francesco Passiglia, Medical Oncology Unit, Department of Surgical, Oncological and Oral Sciences, University of Palermo, Palermo, Italy, testing for epidermal growth factor (EGFR) mutation in circulating tumor DNA (ctDNA) isolated from the plasma of patients with

non-small cell lung cancer (NSCLC), has lower sensitivity compared with standard tissue genotyping but the presence of extrathoracic (M1b) disease may enhance the ability to identify EGFR mutations in plasma. He presented findings from a pooled analysis evaluating the association of metastatic site location to the sensitivity of ctDNA analysis. The investigators searched PubMed, Cochrane Library, American Society of Clinical Oncology, and the World Conference of Lung Cancer meeting proceedings for all published studies evaluating the sensitivity of plasma-based EGFR-mutation testing. They stratified the data of 1233 patients participating in 7 studies by metastatic site location of extrathoracic (M1b) versus intrathoracic (M1a).

Analysis of these pooled data showed the sensitivity of EGFR-mutation testing by ctDNA in patients with NSCLC was significantly higher in patients with extrathoracic disease (M1b) compared to patients with intrathoracic (M1a) disease (pooled odds ratio 4.29; 95% confidence interval 2.20, 8.38). Passiglia *et al.* Abstract 148P

Practice point and future research opportunities

Findings from this analysis of pooled data suggest that the location of metastatic sites significantly influences the diagnostic accuracy of EGFR-mutation testing in ctDNA from plasma. The sensitivity of identifying EGFR activating mutations in the plasma of patients with NSCLC was higher in extrathoracic versus intrathoracic disease, which could influence the clinical management of EGFR-mutated patients.

PD-L1 expression patterns in metastatic tumours to the lung compared with primary NSCLC

Zoran Gatalica, Caris Life Sciences, Phoenix, USA, and colleagues compared the distribution and expression of PD-L1 in a large cohort of 176 advanced tumours that had metastasised to the lungs compared to 81 primary lung non-small cell carcinomas (NSCLC).

PD-L1 expression was assessed by immunohistochemistry using the SP142 antibody (Ventana). PD-L1 positivity was defined as 2+ intensity at $\geq 5\%$ in tumour cells (TC) or immune cells (IC). All cases were stratified into 4 categories based on the expression presence or absence of PD-L1 expression on tumor or IC cells. PD-L1 expression was correlated with total mutational load (TML) measured in tumours using next generation sequencing (NGS).

Primary NSCLC TC showed significantly higher PD-L1 positivity of 28% compared to 14% in metastatic tumours ($p = 0.009$) The opposite was true for IC expression where PD-L1 expression was detected in 28% of metastatic tumours compared to 0% in the primary IC ($p < 0.001$); IC PD-L1 expression ranged from 0% in metastatic renal cell carcinomas to 36-38% in metastatic breast, colon carcinomas, and melanoma. This yielded different stratification patterns based on PD-L1 distribution (TC versus IC), between the primary and metastatic tumours ($p < 0.001$). PD-L1 expression was double positive in both cells types (TC-positive, IC-positive) in 8 metastatic tumours but not NSCLC. Both cell types were negative for PD-L1 expression (TC-negative, IC-negative) in 58 NSCLC and 111 metastatic tumours. PD-L1 expression in tumour but not immune

cells (TC-positive, IC-negative) was detected on 23 NSCLC and 12 metastatic tumour samples. Finally, PD-L1 expression on TC-negative, IC-positive was not observed in NSCLC but was detected on 41 metastatic tumour samples.

The mean TML (\pm standard deviation) in NSCLC was 10 (\pm 5.6) compared to 6.6 (\pm 2.7) in metastatic carcinomas from other sites ($p = 0.013$). The authors also reported that some metastatic cancers, such as triple-negative breast, head and neck carcinoma, and melanoma exhibited higher TC PD-L1 expression. Gatalica *et al.* Abstract 149P

Practice point and future research opportunities

The role of PD-L1 expression as a prognostic factor for response to immune checkpoint inhibitor therapy is controversial; although PD-L1 expression on tumour and/or immune cells has been associated with a more favourable therapy response, response has also been reported in tumours with low to no PD-L1 expression. These findings indicate that a substantial proportion of metastatic tumours to the lung exhibit PD-L1 expression on either tumor or immune cells and may potentially be responsive to treatment with immune checkpoint inhibitors.

RELATED INFORMATION

[Click here to access the Conference abstracts.](#)

[Click here to access the meeting webcast page.](#)

Affiliations and Disclosure

Affiliation

Dr Svetlana Jezdic, ESMO Head Office.

Disclosure

No conflicts of interest to disclose.

Acknowledgement

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

ESMO would like to thank Gilles Defraene, Rajiv Kumar, Giulia Mazzaschi, and Karen L. Reckamp for giving their permission to publish the images from the studies presented during the 2017 ELCC in the ESMO Scientific report.

© Copyright 2017 European Society for Medical Oncology. All rights reserved worldwide.