2018 EUROPEAN LUNG CANCER CONFERENCE (ELCC)

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Geneva, Switzerland

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Summary

The eight edition of the European Lung Cancer Congress (ELCC) welcomed 2135 participants 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 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 2018 follows.

INTRODUCTION

The eighth European Lung Cancer Congress (ELCC) 2018 was held in Geneva, Switzerland from 11 to 14 April. The meeting was organised by the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC), together with their partner societies the European Society for Radiotherapy & Oncology (ESTRO) and the European Thoracic Oncology Platform (ETOP). These organisations united to provide a platform to hear and discuss the latest on patient care, including prevention, diagnosis, treatment, and research in the field of lung cancer.

As usual, ELCC 2018 was well attended, with 2135 participants (1755 delegates, 103 faculty members, 239 industry related participants, and 38 members of the press) travelling from 77 countries. The three countries represented by the highest percentage of attendees were China (13.2%), Switzerland (10.0%), and the United States of America (8.0%). Overall, 65% of the participants were from Europe, 22.3% from Asia, 8.6% from North America, 1.6% from Central and South America, 1.2% from Africa, and 1.1% came from Australia and the Pacific.

The majority (80.2%) of participants who gathered for exposure to the latest developments in lung cancer research and clinical practice were clinicians, but ELCC delegates also included basic scientists (11.7%) and pharmacists (4.5%), with medical students and nurses accounting for approximately 1% each of the delegates. Patient advocates, (0.2%) undergraduate science students (0.2%), and statisticians (0.9%) also contributed to the delegate population.

The occupations most often listed by delegates included medical oncologist (39.9%), pulmonologist (9.0%), medical staff (8.3%), and clinical oncologist (8.1%). Industry representatives, radiation oncologists, basic researchers, clinical researchers, surgical oncologists, chest physicians, pathologists, haemato-oncologists, and biologists made up from 4.7% to 1.2% of the congress participants' occupations. This diversity of profession was reflected in the areas of interest they expressed, which ranged from non-small cell lung cancer (NSCLC; 62.4%), small-cell lung cancer (SCLC; 43.8%), all chest malignancies (43.5%), mesothelioma (24.3%), and thymic carcinoma and thymoma (15.4%).

The most frequently mentioned topics of interest covered the field of oncology ranging from clinical research (43.8%) to staging procedures (13.5%). Many delegates (42.1%) expressed interest in anticancer agents and 38.8% cited cancer biology as a primary interest. Biological therapy and immunotherapy were each mentioned as topics of interest by 32.1% of participants, while 29.7, 27.5%, and 25.0%, respectively, of delegates expressed interest in tumour immunology, molecular pathology, and translational research. The delegates came to hear updates on many other topics, including prevention, epidemiology, precision medicine, basic science, imaging techniques, aetiology, and radiation oncology.

The topics of interest expressed by the participants were addressed by the varied scientific programme, which included 224 accepted abstracts submitted by investigators, with many of them coming from around the world to share their latest research. Some abstracts (16) were chosen for oral presentation and 22 for poster discussion, which featured faculty that placed

abstract findings into clinical perspective and discussed how the results may impact the current standard of care. A total of 186 abstracts were presented as poster presentations, with many of the authors standing by to answer questions and offer additional insight. The abstracts, many describing cutting edge research and the most current treatment strategies, were primarily focused on advanced NSCLC (31.8%), followed by tumour biology and pathology (13.8%), and early stage NSCLC (7.2%). Some abstracts reflected research in locally advanced NSCLC, metastases to and from the lung, SCLC, translational research, mesothelioma, as well as imaging and staging. The topics of prevention, early detection, epidemiology and tobacco control accounted for 8.2% of abstracts and a composite of miscellaneous topics comprised 9.8% of the accepted abstracts.

ELCC brought together recognised leaders in the field of thoracic oncology to present a comprehensive scientific programme that was designed by medical oncology experts to ensure widespread multidisciplinary and multi-professional appeal. The programme included industry sponsored satellite sessions, educational sessions, symposia, and abstract presentations that offered continuing medical education to practitioners across the broad field of lung cancer. The abstracts have been published as a supplement of the Journal of Thoracic Oncology, the official scientific journal of the IASLC. Following is a synopsis of some of the studies presented during ELCC 2018.

TUMOUR BIOLOGY AND PATHOLOGY

Analysis demonstrates nivolumab treatment provides a favourable immune profile in advanced NSCLC

Giulia Mazzaschi, Department of Medicine and Surgery, University Hospital of Parma, Parma, Italy and colleagues identified prognostic and potentially predictive immune profiles in patients with non-small cell lung cancer (NSCLC) being treated with nivolumab. Samples were taken at baseline (T0), and after 2 (T1) and 4 (T2) cycles of bi-weekly nivolumab. The investigators performed an integrated analysis of tissue and peripheral blood samples obtained from 31 patients with advanced NSCLC. FACS evaluation was utilised to assess the number of CD3, CD8, CD4, NK, T-regulatory, and myeloid derived suppressor cells (MDSC), including CD14pos/CD33pos/DRneg. PD-1, CD3ζ, Granzyme B, Perforin, Ki67 and tumour infiltrating lymphocytes (TILs) subpopulations were investigated using immunohistochemistry. These parameters were evaluated to determine their association to clinico-pathological features, response to treatment (RECIST v1.1) and survival outcomes.

Patients with adenocarcinoma (ADC) showed higher levels of T cells in the peripheral blood compared to patients with squamous cell carcinoma (SqCC) ($p < 0.01$). Greater numbers of CD3, CD8, CD4, and NK cells were seen in samples with KRAS mutation, which also shower fewer MDSC ($p < 0.05$). Samples from patients who were active smokers and chronic obstructive bronchopneumopathy directly correlated with T and NK cells proliferation ($p < 0.05$). In addition, increased effector and reduced immune suppressive phenotypes were observed in samples from steroid naive patients ($p < 0.05$).

Samples from 19 patients showing clinical benefit following nivolumab had a distinctive baseline peripheral blood immune profile that included higher numbers of NK, CD3ζ-positive, Pfn-positive, GrzB-positive, and CD8-positive/PD-1-positive cells ($p < 0.01$) than samples from 12 non-responding patients. This profile of immune features was maintained during nivolumab treatment. However, during treatment, the MDSC levels progressively rose in non-responders ($p < 0.05$). Patients with high NK and CD8-positive/PD-1-positive number at baseline showed longer overall survival (OS) ($p < 0.05$) and progression-free survival (PFS; $p < 0.01$).

Tissue analysis showed a high PD-L1 score correlated with modest clinical impact. However, low PD-1 expression in CD8-positive TILs was observed in samples from responders compared to non-responders ($p < 0.001$) and showed a non-significant association with prolonged OS and a significant association with improved PFS ($p < 0.01$).

Taken together, baseline peripheral blood samples with high NK and CD8-positive/PD-1-positive and tissue samples with low CD8-positive/PD-1-positive indicated positive prognostic factors characterising an immune privileged profile that associated with significantly prolonged PFS ($p < 0.001$) and OS ($p < 0.01$). Mazzaschi *et al*. Abstract 1O

Practice point and future research opportunities

PD-1 expression in blood and tissue cytotoxic cells associated with a preserved functional pool of circulating NK cells and specific factors identified in baseline samples characterised an immune profile that associated with nivolumab efficacy.

MET activation is independent of the JAK-STAT pathway and contributes to an immunosuppressive phenotype in NSCLC

Maria Saigí, Genes and Cancer Group, Bellvitge Biomedical Research Institute, Barcelona, Spain, investigated the role played by somatic genomic alterations in the ability of tumour cells to escape immune surveillance checkpoints. Using samples from 155 primary resections of non-small cell lung cancer (NSCLC), the investigators examined the mutation status of known recurrent driver genes in lung cancer, including *EGFR, KRAS,* and *MET*. They also determined expression of immune-related molecules, such as PD-L1, the HLA-complex, and CD8-positive tumour infiltrating lymphocytes (TILs). The association of genomic alterations with immune markers was evaluated by Chi-square testing and validated in genetically characterised cancer cell lines. Functional assays were performed using appropriate treatments, including IFNγ, to modulate the selected pathways, and RNA-Seq analysis was done to analyse differential gene expression with these treatments.

Three percent of the lung cancer samples showed *MET* activation (*MET* exon 14 skipping mutations) and *MET* amplification. These tumours were also more likely to have positive immunostaining (≥5%) of PD-L1 ($p = 0.05$); however, these samples had no specific CD8-positive TILs pattern. Analysis of *MET* altered cancer cell lines revealed PD-L1 was upregulated through *MET* activation that was independent of the JAK-STAT pathway. Lung cancer cell lines containing *JAK2* loss of function mutations co-occurring with *MET* alterations abrogated the response to IFNγ.

Genes involved in negative regulation of immune response, such as *CD274* (PD-L1), *PDCD1LG2* (PD-L2), *SOCS1,* and *SOCS3* were found to be included in the *MET* activated signature and IFNγ treatment, according to RNA-Sequence analysis. However, none of the pro-immune response genes commonly found in IFN-Signature were upregulated in the *MET* activation-Signature. Saigli *et al.* Abstract 2O

Practice point and future research opportunities

MET oncogenic mutation is not mutually exclusive with JAK2 inactivating mutations in lung cancer and promotes the intrinsic expression of several negative checkpoints of the immune response, including PD-L1. Both genetic alterations lead to immune tolerance and are likely to promote tumour growth.

Co-targeting PIM1 or Src to overcome the limits of single MET inhibition

Ilaria Attili of the Istituto Oncologico Veneto IRCCS, Padua, Italy and a team of investigators continue to explore the mechanism of resistence to MET in MET addicted tumours. The team previously identified overexpression of receptor tyrosine kinases (RTKs), like AXL and the transmembrane protein CUB domain-containing protein-1 (CDCP1), as well as Src activation, as components in the mechanisms of intrinsic resistance to epidermal growth factor receptor (EGFR) inhibition in EGFR mutant lung cancer. In this study, they investigated the effect of single MET inhibition in MET addicted tumour cell lines. They tested whether the expression and activation of RTKs, SHP2 or CDCP1 are driven by PIM1 or Src, resulting in resistance to MET inhibitors in MET addicted tumours. With MET inhibition, the proviral integration site for the Moloney murine leukaemia virus-1 (PIM1) is activated in MET addicted cells; PIM1 then drives the expression of RTKs. SHP2, a non-receptor protein tyrosine phosphatase, is central in RTKs signaling and in Src activation.

The investigators used the class I MET inhibitors tepotinib and savolitinib, the pan-PIM inhibitor AZD1208, and the Src inhibitor dasatinib in 5 MET addicted cell-lines; 2 cell-lines were MET amplified lung cancer cells (EBC1 and H1993), 2 were MET exon 14 mutant cells (Hs746T and H596) and one was a glioma cell-line that carries the MET exon 7-8 splicing variant (E98). They assessed the effect of combined MET and PIM or MET and Src inhibition on cell viability and protein expression using immunoblotting.

All of the cell lines, except H596, (MET exon mutation positive) showed sensitivity to single MET inhibition and were resistant to single AZD1208 or dasatinib. Combining savolitinib or tepotinib with AZD1208 was synergistic in the EBC1 cell line and slightly synergistic or additive in the H1993, Hs746T and E98 cell lines. The combination of savolitinib or tepotinib with dasatinib was highly synergistic in all four cell-lines. The treatment of EBC1 cells with tepotinib monotherapy did not inhibit AXL activation, while it induced the activation of SHP2 and CDCP1. Tepotinib combined with dasatinib downregulated expression or activation of AXL, CDCP1 and SHP2. Attili *et al.* Abstract 3PD

Practice point and future research opportunities

These findings using MET addicted cell-lines demonstrated that co-targeting PIM or Src with MET may be more effective than MET inhibition alone in MET. Overexpression and activation of RTKs, CDCP1 and SHP2 can be mechanisms of resistance to single MET inhibition. The investigation of combinatorial strategies in MET addicted tumours, merits further investigation.

PREVENTION, EARLY DETECTION, EPIDEMIOLOGY, TOBACCO CONTROL

Case-control study determines the risk of lung cancer in women associated with exposure to biomass fuel smoke

Renata Baez-Saldana, Respiratory Oncology, Instituto Nacional de Enfermedades Respiratorias, Ciudad de México, Mexico, pointed out that, along with smoking, exposure to carcinogens from indoor solid fuel use also constitutes a substantial risk factor for lung cancer, with approximately 1.5% of annual lung cancer deaths being attributed to this carcinogen. There are limited data on lung cancer risk associated with exposure to biomass fuel smoke, especially in women, prompting Dr. Baez-Saldana and her team design this study, which aimed to estimate the risk of lung cancer in women according to the magnitude of exposure to biomass cooking fuel smoke. This hospital-based case-control study compared 136 cases of confirmed primary lung cancer with 137 hospital controls having various lung and respiratory diseases. In the control cohort, 50 (27%) participants had interstitial lung diseases, 46 (25%) had pulmonary tuberculosis, 43 (24%) had pneumonia, 33 (18%) had pulmonary embolism, and 11(6%) controls had ear, nose and throat ailments.

Exposure to wood smoke was assessed as a continuous variable based on the calculation of exposure multiplied by average hours of exposure per day that was expressed as hour/years, as a categorical variable that was stratified into three categories (<100, 101 to 299, and > 300 hour/years), or as ‘any’ or ‘none’. The investigators used unconditional logistic regression to compute odds ratio (OR) and 95% confidence intervals (95% CI) for the lung cancer risk associated with biomass cooking fuel smoke exposure, adjusting for potential confounders, such as tobacco use, age, gender, and socioeconomic level; this analysis was repeated with only non-smoking women.

This analysis found that cases were older than the controls, with a median age of 65 compared to 62 years old ($p < 0.05$). Patients with lung cancer had a higher rate of exposure to wood smoke (REWS) of 144 compared to 88 hour-years for controls ($p < 0.05$). The risk of lung cancer increased in a linear fashion as hour-years of exposure increase, OR 1.02 (95% CI, 1.00-1.00; $p = 0.019$). The crude odds ratio for exposure of more than 100 hour-years was OR 1.66 (95% CI, 0.76-3.64) and the adjusted odds ratio for the same exposure was OR 2.19 (95% CI, 0.89-5.40). The crude odds ratio for lung cancer in patients having more than 300 hour-years rose to OR 1.78 (IC95% 0.77-4.13) and the adjusted OR was 3.01 (95% CI, 1.12-8.36). In non-smoking women at this exposure, the risk increased to OR 5.71 (95% CI, 1.33-24.60). These associations remained after adjusting for sex, smoking, socioeconomic status, and housing with asbestos sheet roof. Baez-Saldana, *et al.* Abstract 35PD

Practice point and future research opportunities

Findings from this analysis raise awareness of the magnitude of exposure to biomass smoke expressed in hour-years constitutes a risk factor for developing lung cancer that may be sizable in regions of the world. The risk of lung cancer from wood smoke exposure was higher in non-smoking women.

Younger individuals, women and non-smokers should be included in low-dose spiral computed tomography lung cancer screening programmes

Xiaoyang Luo, Thoracic Surgery, Fudan University Shanghai Cancer Centre, Shanghai, China and collegues determined the efficacy of early lung cancer screening with low-dose spiral computed tomography (LDCT) in individuals with varying degrees of lung cancer risk. Over a 5-year period beginning in November 2012 the investigators screened 2516 men and 3787 women in three hospitals in Shanghai City for early diagnosis of lung cancer with LDCT. Individuals with lung cancer were offered multidisciplinary comprehensive treatment, including minimally invasive surgery, prevention, diagnosis, treatment, rehabilitation, and follow-up.

Screening resulted in a diagnosis of primary lung cancer in 126 individuals, providing a detection rate of 170.9/100,000, and 219.2/100,000 among the male and female participants, respectively ($p = 0.180$). The detection rate among non-smokers was 207.6/100,000 compared to 183.5/100,000 among smokers ($p = 0.524$). In older participants aged 60 years and more, the detection rate was 181.7/100,000, and 200.5/100,000 in participants aged 22 to 40 ($p = 0.703$). Luo *et al.* Abstract 36PD

Practice point and future research opportunities

These findings from a 5-year lung cancer screening programme in East Asia provides new demographic characteristics with higher than expected detection rates among females, non-smokers, and people between the age of 22 and 40 compared to the traditional-sense high risk population. Females, non-smokers, and people between the age of 22 and 40 should not be excluded from screening with LDCT.

TRANSLATIONAL RESEARCH

An analysis of MEK inhibition on PDL1 expression and on cytokine production in NSCLC cell lines and human lymphocytes

Floriana Morgillo, AOU Seconda Università degli Studi di Napoli (AOU-SUN), Naples, Italy and colleagues investigated changes in the MAPK signalling cascade, a key intracellular signaling network that transduces multiple proliferative signals that contribute to tumorigenesis and metastasis following PDL1 blockade. They began by determining levels of PD-L1 mRNA expression using Real Time qPCR, as well as the protein levels of PD-L1 and MAPK proteins, by western blot analysis in a panel of non-small cell lung cancer (NSCLC) cell-lines. They studied the changes in PD-L1, major histocompatibility complex class-I (MHC-I) expression and the production of cytokines following inhibition or stimulation of MAPK signalling using selumetinib, a MEK inhibitor, or stimulation by phorbol 12-myristate 13-acetate (PMA). They also investigated the effect of MEK inhibition on T-cell function in peripheral blood mononuclear cells (PBMC) from healthy volunteers.

A consistent pattern between PD-L1 mRNA and PD-L1 protein expression across cell lines was observed by RT-qPCR and Western blot analysis in the panel of NSCLC cell-lines, which suggested to the investigators that PD-L1 expression mainly depends on transcriptional regulation, together with activated MAPK and MEK1/2 signals. After 24 hours of MEK inhibitor treatment of these cell-lines, a significant decrease of PD-L1 mRNA and protein levels was observed, suggesting that the MAPK signal contributes to PD-L1 expression. Consistently, MEK inhibitor treatment decreased the activation of PD-L1 promoter by p65. Using PMA treated cells as a control, the investigators observed significant increase of PD-L1 mRNA levels with this treatment, further supporting the role of MEK as a modulator of the immune microenvironment. MEK inhibition also yielded increased expression of MHC inhibitor on cancer cells, as well as increased levels of mRNA expression of IFN gamma, IL-6, IL-1B, and TNF alpha, which all participate in the activation and differentiation of the TCD8-positive cytotoxic lymphocytes (CTL) subset.

A RT-qPCR analysis of the effect of MEK inhibitor on activated T-lymphocytes obtained from the PBMC of healthy volunteers revealed a significant increase of mRNA expression of typical CD8-positive T cell pro-inflammatory cytokines, including IL-12, TNF alpha and IFN gamma after five days of MEK inhibitor treatment. Morgillo *et al.* Abstract 51PD

Practice point and future research opportunities

Findings from this analysis of NSCLC cell-lines and human lymphocytes support that MEK inhibition induces blocking of PD-L1 expression, thus establishing a proinflammatory microenvironment by upregulation of MHC inhibitor on cancer cells and stimulating cytokines that promote CD8-positive CTL activation. Following selumetinib treatment of peripheral T cells, levels of pro-inflammatory cytokines typical of the CTL subset were increased. The investigators suggest MEK inhibition may represent a potential mechanism to convert resistant tumours to

treatment sensitive tumours by potential treatment strategies combining MEK inhibitors with anti-PD-L1 antibodies in NSCLC.

An analysis of EGFR clonality and tumour mutation burden in paired blood and tissue samples based on circulating tumour DNA sequencing in advanced NSCLC

Xinghao Ai, Lung Tumour Clinical Medical Centre, Shanghai Chest Hospital, Shanghai, China, presented findings from a prospective multicentre clinical trial to determine whether clonality of sensitive mutation in tumours from patients with non-small cell lung cancer (NSCLC) may be related to the efficacy of tyrosine kinase inhibitor (TKI) treatment. The investigators also evaluated the relationship of tumour mutational burden (TMB) between tissue and blood. This analysis used paired tumour and plasma samples obtained at diagnosis from 80 patients from 9 centres with advanced NSCLC who were naive to systemic treatment.

DNA was sequenced by target-capture deep sequencing of 1021 previously annotated genes related to solid tumours. Clonal EGFR mutation was defined as EGFR mutations in the cluster with the highest mean variated allele frequency with PyClone; other EGFR mutations were classified as subclonal EGFR mutation. The analysis of TMB in tissue and blood samples included single nucleotide variants, small insertion and deletion, with variant allele frequency (VAF) ≥3 % and ≥0.5%. TMB-high patients were identified with ≥9 mut/MB (upper quartile of data from geneplus).

The analysis uncovered 371 somatic variations in tissue samples, with the most frequently occurring mutations observed in TP53 (52 %), EGFR (47 %), ALK (13 %), and KRAS (11 %). In matched plasma samples, 258 (70 %) tumour-derived mutations were detected by pan-cancer panel sequencing. In 37 patients, 41 EGFR mutations were detected, which mostly occurred in the tyrosine kinase domain (Ex19del, 42%; L858R, 37%). Most EGFR mutations were clonal in both tissue and plasma, with a consistency of 85% in paired samples. In addition, the TMB in blood significantly associated to the tissue TMB (Pearson r= 0.75, p = 2.3e-12) with 90% consistency. Interestingly, high TMB was observed in a small fraction (6%) of patients having driver mutations, such as mutations in EGFR, ALK fusion, ERBB2, and PIK3CA. NCT03059641. Ai *et al.* Abstract 52PD

Practice point and future research opportunities

Deep sequencing with the pan-cancer panel can effectively detect mutations and evaluate TMB in both tissue and blood with high consistency. EGFR mutations can be clonal or subclonal in both tissue and blood. This prospective study is ongoing to determine whether EGFR clonality may serve as a predictive factor for TKI efficacy in NSCLC.

IMAGING AND STAGING

Initiative links emergency department incidental lung nodule findings to patient follow-up

Kenneth A. Lee, Thoracic Surgery, Jupiter Medical Centre, Jupiter, USA discussed the lung nodule best practice initiative that was evaluated and incorporated into the Jupiter Medical Centre. The initiative coordinates the emergency department visits where a lung nodule is detected to follow-up care post discharge. The process includes an assessment of the chest computed tomography (CT) scan after completion of an evaluation done in the emergency department. With detection of a lung nodule the patient is made aware of the findings by emergency department clinician who then documents the finding by choosing a box in the electronic medical record (EMR) reporting lung nodule detected prior to emergency department discharge. This automatically generates a daily email to the thoracic nurse navigator who contacts the patient to offer either an appointment to the lung nodule clinic, an assignment with primary physician, or patient declined options. This decision is documented as conclusion in the EMR and a certified letter is sent to the patient as a recommendation and summary.

The emergency department lung nodule report listed 287 patients from the first of November 2016 to the 31st of December 2017. Of these, 45 patients did not have a true nodule and were excluded from this audit. Of the 242 remaining patients, 12 (4.9%) patients were referred to the Lung Centre Nodular Clinic and 176 (72.7%) patients were referred to other physicians, such as pulmonary and primary care physicians. A total of 54 (22%) patients either declined follow-up or were unable to be reached. Therefore, a follow-up referral was made for 78% of incidental pulmonary nodules from the emergency department.

This audit revealed 2 days of blank reports from the emergency department, leading to review of reports from radiology and the emergency department that were compared for the week of November 20-27, 2017. A total of 31 patients with nodules on radiology reports were missing from the emergency department version: 18 from the day shift and 13 on night shift, indicating that more nodule patients may not have been accurately reported. Since the emergency department account relies on manual check box, the thoracic nurse navigator now runs emergency department reports against the radiology versions to double-check the correct number of patients with incidental pulmonary nodules. Lee *et al.* Abstract 51PD

Practice point and future research opportunities

Many incidental lung nodules are discovered nationwide in the US and elsewhere through the emergency department, with many patients going without follow up. This study demonstrates an initiative that implements a verifiable system along the pathway beginning in the emergency department through discharge.

Magnetic resonance imaging of NSCLC brain metastases may provide potential biomarkers for EGFR status

A team of investigators, including lead author, Abhishec Mahajan of the Tata Memorial Hospital Centre, Mumbai, India performed an analysis of magnetic resonance imaging (MRI) biomarkers of brain metastases in patients with non-small cell lung cancer (NSCLC) to determine their association to molecular subtyping of EGFR status and to correlate these imaging features with response to therapy and clinical outcomes. They reviewed the clinical data of 75 patients who were tested for epidermal growth factor receptor (EGFR) mutation and underwent brain multiparametric magnetic resonance imaging (MRI) at diagnosis; 38 patients were EGFR mutation-positive and 37 EGFR were EGFR mutation-negative. Logistic regression multivariate analysis was used to determine associations between EGFR mutation status and clinical features, specifically age, sex, smoking, TNM stage, and imaging variables, and brain metastasis.

Patients who were EGFR mutation-positive showed early and wide-spread development of brain metastasis within 6 months after the first presentation ($p = 0.00$). EGFR mutated also showed a statistically significant difference in border/margins on T2W imaging, fuzzy and infiltrative borders compared with well-defined border/margins in EGFR negative patients ($p = 0.00$). The incidence of recurrent metastatic disease and meningeal involvement was significantly higher in EGFR positive versus EGFR mutation negative patients, respectively ($p = 0.00$ and $p = 0.04$).

EGFR wild-type patients showed focal restriction on DW images ($p = 0.001$) and also demonstrated good response to whole brain radiation therapy ($p < 0.00$). On multivariate analysis, a statistically significant association was found between T2 border, number, restricted diffusion, meningeal positivity, and time to progression ($p < 0.05$). Mahajan *et al.* Abstract 72PD

Practice point and future research opportunities

The brain is a common site of metastases with EGFR mutated lung cancer. This study contributes to the literature on MRI metrics or feature analysis of NSCLC brain metastasis. EGFR mutation-positive brain metastases have characteristic MRI features that can may serve as non-invasive diagnostic, predictive and prognostic imaging biomarkers. These MRI based biomarkers have a potential role in personalised therapy of EGFR positive brain metastasis in NSCLC.

SMALL-CELL LUNG CANCER

FOXP3-positive tumour infiltrating lymphocytes may play a prognostic role in patients with SCLC

Alberto Pavan, Medical Oncology 2, Instituto Oncologico Veneto IRCCS, Padua, Italy and collegues performed a retrospective analysis of tissue samples from 104 patients with small-cell lung cancer (SCLC) using immunohistochemistry (22C3 clone, DAKO) to evaluate levels of PD-L1 expression on tumour cells (TCs) and on tumour infiltrating lymphocytes (TILs). Positivity was defined as PD-L1 expression on 1% or more TCs or TILs. They also did immunohistochemistry for CD8 (C8/144B clone, DAKO) and FOXP3 (236A/E7 clone, ABCAM) to categorise CD8 and FOXP3 TILs as positive versus negative using a semi-quantitative score. Surgical resection had been done in 48 patients, 18 patients had been treated with radical-intent chemo-radiotherapy, and 38 patients had metastatic disease.

Overall, PD-L1 was expressed on TCs in 25% of samples. PD-L1 expression significantly associated with disease stage: 32% stage I-III, 13% metastatic stage ($p = 0.034$ for TCs and $p = 0.002$ for TILs). PD-L1 positivity also associated with outcome: Median overall survival (OS) was 46.8 months (95% confidence interval [CI], 22.6-71.0) in patients with positive PD-L1 expression compared to just 10.9 months in patients with negative PD-L1 expression (95% CI, 6.2-15.7; $p = 0.047$). This relation with outcome was not confirmed in multivariate analysis.

CD8-positive TILs and FOXP3-positive TILs were present in 59% and 72% of samples respectively. The presence of CD8-positive TILs or of FOXP3-positive TILs did not correlate to stage. However, the presence of FOXP3-positive TILs was associated with improved prognosis among non-metastatic patients who demonstrated median OS of 52.5 months (95% CI, 21.4-83.7) compared to 20.5 months in patients with FOXP3- negative TILs (95% CI, 0-49.2; $p = 0.027$); this association was confirmed in multivariate analysis. Pavan *et al.* Abstract 78O

Practice point and future research opportunities

SCLC represents one of the most aggressive lung malignancies and is characterised by a high growth fraction and early metastatic spread, creating a high unmet need for new therapeutic options. Although immunotherapy may be promising approach, no molecular prognostic markers have been validated for clinical practice thus far, and data on the immune microenvironment in SCLC are limited.

This study showed that PD-L1 expression is reduced in advanced stage SCLC patients. Further studies are needed to understand if this down-regulation of PD-L1 is linked to a more aggressive phenotype. The putative prognostic role of FOXP3 TILs in stage I-III SCLC also warrants further confirmation in larger series of patients.

EARLY STAGE NON-SMALL CELL LUNG CANCER

Nomogram identifies stage I lung adenocarcinoma patients at high risk of recurrence that may benefit from adjuvant chemotherapy following complete lobectomy

Jiang Qian, Shanghai Chest Hospital, Shanghai, China presented findings from a retrospective study designed to develop a recurrence risk-scoring model in stage I lung adenocarcinoma following complete lobectomy, and to identify and assess the high-risk population that would benefit from adjuvant chemotherapy.

This analysis included 4606 patients with pathologically confirmed stage I lung adenocarcinoma who underwent complete lobectomy at the Shanghai Chest Hospital from 2008 to 2014. The non-adjuvant chemotherapy cohort comprised 3514 patients and 1092 patients were in the adjuvant chemotherapy cohort. The nomogram was developed in the non-adjuvant chemotherapy cohort and Cox proportional hazards regression was used to predict 5-year recurrence-free survival (RFS). The predictive value was compared between the nomogram and the 8th edition of TNM system. Identification of the patient population that benefited from adjuvant chemotherapy was determined by comparing RFS between the non-adjuvant chemotherapy and the adjuvant chemotherapy group, as stratified by the TNM stage, risk score quartiles and 5-year recurrence probability, respectively. The optimal cut-off scores were determined using X-tile software.

This analysis determined 6 independent predictors of recurrence that included age, gender, tumour size, pathological subtype, the presence of visceral pleural invasion (VPI), and lymphovascular invasion (LVI). The RFS prediction was more accurate by nomogram than the TNM staging, C-index: 0.784 (95% confidence interval [CI], 0.756–0.812) compared to 0.719 (95% CI, 0.689–0.749), respectively ($p = 0.0017$). A non-statistically significant trend towards benefit with adjuvant chemotherapy was observed that paralleled the increasing risk scores.

A 50% recurrence score was the breakpoint for improved RFS after adjuvant chemotherapy, with patients having a 50% recurrence probability demonstrating long RFS compared to patients with a lower recurrence score ($p = 0.0286$). The optimal cut-off of the risk score was set at 203 and 244; adjuvant chemotherapy was detrimental in patients with risk scores below 203 ($p < 0.0001$) and beneficial in those with risk scores above 245 ($p = 0.0416$). Patients with score ≥ 245 accounted for 0.4% of stage IA patients and 7.5% of stage IB patients, respectively. The subgroup comprising 62.8% of stage IB patients with predominant solid/micropapillary subtype contained the most patients having a score ≥ 245, who benefited the most from adjuvant chemotherapy. Qian *et al.* Abstract 91O

Practice point and future research opportunities

The nomogram provided an accurate RFS prediction for patients with lobectomised stage I lung adenocarcinoma by identifying a high-risk population with a recurrence risk score ≥ 245 that may benefit from postoperative adjuvant chemotherapy.

Meta-analysis shows adjuvant TKI therapy delays disease progression in EGFR mutated NSCLC

Jacques Raphael, Oncology, London Regional Cancer Centre, London Health Science Centre, University of Western Ontario, London, Canada and colleagues conducted this review and meta-analysis to evaluate the efficacy and safety of adjuvant treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) in non-small cell lung cancer (NSCLC). They searched Medline and EMBASE to identify relevant randomised trials conducted from January 2000 to October 2017; 6 studies met the inclusion criteria. Pooled hazard ratios (HR) for disease-free survival (DFS) and overall survival (OS), and pooled risk ratios (RR) and odds ratios (OR) for 2-year DFS and toxicity were extracted using the generic inverse variance and the Mantel-Haenszel and Peto method to perform a meta-analysis. Subgroup analyses assessed patients with a sensitising EGFR mutation.

In patients with EGFR mutated NSCLC, analysis of data from 5 trials comprising 560 patients showed that adjuvant TKI treatment decreased the risk of disease recurrence by 48%, hazard ratio (HR) 0.52 (95% confidence interval [CI], 0.35-0.78). Data from 6 trials with 599 patients showed improved 2-year DFS, HR 0.53 (95% CI, 0.43-0.66) with adjuvant TKIs; however, data from 4 trials with 662 patients revealed no overall OS effect with this treatment, HR 0.64 (95% CI, 0.22-1.89).

This analysis also revealed that adjuvant TKIs treatment had little benefit in patients with any EGFR status; in 5 trials including 1860 patients DFS was slightly improved, HR 0.65; 95%CI 0.43-1.00). Four trials with 662 patients with any EGFR status also showed no OS benefit with adjuvant TKIs, HR 0.8 (95% CI, 0.48-1.33).

The analysis also revealed increased adverse events in patients receiving adjuvant TKI therapy. Six trials comprising 1831 patients demonstrated adjuvant TKIs was associated with an increased risk of developing grade 3 or higher skin toxicity, OR 6.07 (95% CI, 4.34-8.51) and diarrhoea OR 4.05 (95% CI, 2.44-6.74) compared to patients receiving chemotherapy, placebo or no treatment. Raphael *et al.* Abstract 133PD

Practice point and future research opportunities

The role of adjuvant EGFR TKIs in NSCLC is not well defined. In this analysis, adjuvant TKI treatment significantly decreased the risk of recurrence in patients with EGFR mutated NSCLC but did not demonstrate an effect on OS. The authors pointed out that OS data were immature and suggested longer follow-up for a definitive assessment of this outcome measure. Further

results from ongoing well-designed trials will define the role of adjuvant TKI in NSCLC and provide stronger conclusions.

LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

Negative impact on short-term health-related QoL after prophylactic cranial irradiation for stage III NSCLC resolves over time

Willem W. Witlox from the Clinical Epidemiology and Medical Technology Assessment Department of Maastricht University Medical Centre, Maastricht, Netherlands presented findings on behalf of a team of investigators from the Netherlands. They used data from the NVALT-11/DLCRG-02 randomised phase III study to compare quality of life (QoL) outcomes in patients receiving prophylactic cranial irradiation (PCI) with patients receiving observation only following chemo-radiotherapy for stage III non-small cell lung cancer (NSCLC).

The NVALT-11/DLCRG-02 study demonstrated that patients receiving PCI had a significant decrease in time to develop symptomatic brain metastases. However, these patients also had more low-grade neurological toxicity, hazard ratio (HR) 0.25; 95% confidence interval (CI), 0.11-0.58), prompting the team to evaluate QoL in 86 patients treated with PCI compared to 88 patients in the observational arm. QoL was measured using the EORTC QLQ-C30 and EuroQol 5D (EQ-5D), which were administered to both cohorts prior to PCI and at 3, 12, and 24 months following PCI. Specifically, functional scales and global health status scores contained in the QLQ-C30 and the VAS and utility scores in the EQ-5D were analysed using non-parametric tests. In all, 853 observations were made.

At baseline, QoL was similar between arms, except for emotional ($p = 0.025$) and cognitive functioning ($p = 0.039$) scores, which favoured the PCI arm. At three months, cancer-specific QoL, as measured on the QLQ-C30, showed that physical and cognitive functioning were significantly better in patients not treated with PCI; scores for physical functioning in the observational arm were median 83 compared to median 73 in the PCI arm ($p = 0.003$). Median cognitive scores were 100 versus 83 in the respective groups ($p = 0.006$), and scores for global disease specific QoL were equivalent at median 67 in both groups. Global health-related QoL assessment using the EQ visual analogue scale (VAS) showed patients receiving observation only scored median 70 points compared to patients receiving PCI who scored median 60 points ($p = 0.017$); EQ-5D utility scores were similar between the groups.

The impact of PCI on QoL lessened in the longer term, where only the cognitive functioning scores of QoL remained lower in patients receiving PCI than patients on observation. Assessments taken at later time-points showed no significant differences in QoL between the groups, except for significantly better cognitive functioning that was recorded at 24 months in the observational arm; these scores were median 83 with observation versus 67 with PCI ($p = 0.017$). At 24 months, no significantly different QoL as reported on the QLQ-C30 or EQ-5D was observed between the two groups.

However, emotional and social scores were equivalent or better in the PCI and observational groups over 3 post procedure time points; median scores for emotional QoL at T3, T12 and T24 months were 83, 83, and 92 for emotional QoL in the PCI group versus 88, 83, and 88 in the

observational arm. The scores for social QoL at these time points were 83, 100, and 83 with PCI versus 83, 83, and 100 with observation. Witlox *et al.* Abstract 109O

Practice point and future research opportunities

Although PCI has been shown to significantly reduce the incidence of brain metastases in patients with stage III NSCLC, PCI may also result in short-term impairment of both generic and disease specific health-related QoL. However, the impact on long term QoL seems to be limited to problems concerning cognitive functioning.

High doses of radiation given as an individualized isotoxic dose chemoradiotherapy strategy may be a treatment option in unresectable NSCLC

Baosheng Li, Shandong Cancer Hospital, Jinan, China and colleagues investigated whether individual isotoxic dose escalation based on normal tissue constraints (NTC) could provide more benefit compared to the standard radiation dose used in concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer (NSCLC). The investigators reviewed pooled data from two prospective clinical trials using individually prescribed radiation doses that were calculated based on NTC. The trials enrolled 140 patients from March 2006 to September 2012. Seventy-one patients receiving total radiation doses ≥66 Gy were included in the high-dose group and the 69 patients receiving < 66 Gy were assigned to the standard-dose group. The primary endpoint of this analysis was overall survival (OS).

Radiation doses greater than 66 Gy delivered in dose-escalation together with concurrent chemotherapy provided significantly improved median survival times and 5-year survival rates over standard-dose radiation in these patients. Patients receiving radiation doses >66Gy demonstrated longer median OS of 33.5 months compared to 17 months in the standard dose group receiving 66 Gy ($p < 0.0001$). In addition, patients in the high dose cohort demonstrated three-fold higher 5-year OS rates of 38% compared to just 12.3% observed in the standard dose cohort. The high dose cohort also showed prolonged median progression-free survival (PFS) of 19 months compared to 11 months in the standard dose group ($p < 0.0001$).

The rates of severe grades 3 to 5 toxicity were similar between the two groups. Li *et al.* Abstract 110O

Practice point and future research opportunities

The RTOG0617 study found that a higher radiation dose did not benefit patients with unresectable stage III NSCLC; however, delivering higher doses using an individualised isotoxic dose chemoradiotherapy strategy may be a promising method for unresectable stage III NSCLC patients. In this study, dose-escalated radiation administered concurrently with chemotherapy showed a significant advantage in survival rates over standard-dose radiation.

Minimising cardiac doses may improve survival in patients with NSCLC receiving radical accelerated radiotherapy

Matthew Hatton, Clinical Oncology, Weston Park Hospital Cancer Research Centre, Sheffield, UK pointed out that the RTOG 0617 trial identified cardiac dose-volume metrics as independent predictors of survival for locally advanced patients with non-small cell lung cancer (NSCLC) following chemoradiotherapy with conventional and dose escalated regimes. Accelerated radiotherapy schedules such as continuous hyperfractionated accelerated radiotherapy (CHART) are widespread in the UK prompting Dr. Hatton and colleagues to study the impact of cardiac dosimetry on survival in patients receiving radical treatment with accelerated radiotherapy for early stage and locally advanced NSCLC. In this retrospective analysis, the records were reviewed of all stage I-III NSCLC patients treated at the Weston Park Hospital Cancer Research Centre with radical accelerated radiotherapy (CHART, 54Gy/36# over 12 days; hypofractionated, 55Gy/20# over 4 weeks) from 2010 to 2015. Patient demographics, tumour characteristics, survival and dosimetric data were recorded. Cardiac dosimetric parameters included heart V5, V30, V33, V50, V67, V100 and mean dose. The impact of these metrics on survival was assessed using Cox regression.

Of the 563 patients treated with accelerated radiotherapy, 294 patients had cardiac dosimetric data. In this cohort, 55% of patients were male with a mean age of 72. Thirty-three percent, 16%, and 51% of patients had stage I, II, and III disease, respectively and 60% had a WHO performance status of 0-1. CHART had been administered to 124 patients and 171 received hypofractionated radiotherapy.

Overall, the 2 year overall survival (OS) was 48% with a median OS of 22.5 months. On univariate analysis, gender, stage, tumour recurrence, PTV volume and all cardiac dosimetric parameters were significantly associated with survival. On multivariate analysis only PTV volume and heart V30, V33, V50 and mean dose remained independent predictors of survival. The mean heart dose was the most predictive of OS (hazard ratio [HR] 1.027, 95% confidence interval [CI], 1.002-1.053; p = 0.032). Hatton *et al.* Abstract 111O

Practice point and future research opportunities

Several cardiac dosimetric parametres were determined to be independent predictors of survival following accelerated radiotherapy, with the mean heart dose emerging as the best predictor of OS. Minimising cardiac dose during radiotherapy may improve outcomes, which warrants further study.

ADVANCED NON-SMALL CELL LUNG CANCER

Post-progression data support moving osimertinib into the first-line setting in EGFR-mutated NSCLC

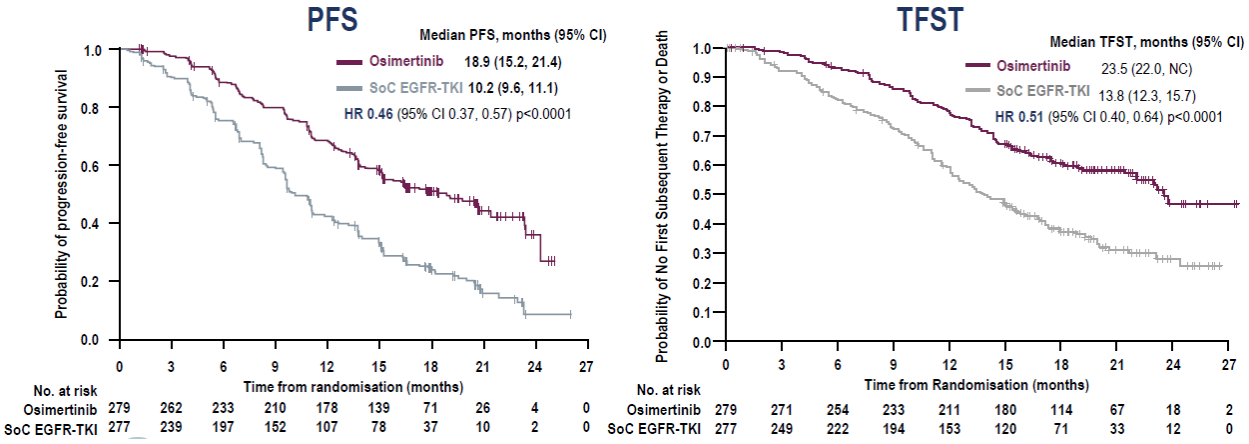
David Planchard, Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France reported exploratory post-progression outcomes on behalf of the FLAURA investigators. FLAURA compared osimertinib with standard of care (SoC) treatment in the first-line setting in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) plus either exon 19 deletion or L858R sensitising mutations in the epidermal growth factor receptor (EGFR). Prof. Planchard reviewed FLAURA findings that showed patients receiving osimertinib had significantly improved progression-free survival (PFS) compared to patients on SoC (hazard ratio [HR] 0.46; 95% confidence interval [CI], 0.37-0.57; $p < 0.001$), as well as improved overall survival (OS), HR 0.63 (95% CI, 0.45-0.88; $p = 0.007$). (Soria JC *et al. N Engl J Med* doi: 10.1056/NEJMoa1713137). Although these interim OS data were encouraging, they were not formally statistically significant at 25% maturity, which required a p-value of < 0.0015 to achieve statistical significance.

FLAURA enrolled 556 treatment-naive patients who were randomised equally to oral osimertinib at 80 mg once daily (n = 279) or to SoC (n = 277), consisting of either oral gefitinib at 250 mg orally once daily or oral erlotinib at 150 mg once daily. Patients continued to receive treatment until disease progression; treatment beyond progression with subsequent therapy was per investigator discretion and patients on SoC were allowed to cross over to osimertinib upon central confirmation of progression and EGFR T790M positivity.

Data of treatment following disease progression revealed fewer osimertinib-treated patients discontinued treatment, experienced disease progression or died. As of the data cut-off on 12 June 2017, treatment was discontinued by 138 (49%) patients in the osimertinib cohort and by 213 (77%) patients on SoC. Of the discontinuing patients, 82 (29%) former osimertinib patients versus 129 (47%) former SoC patients received subsequent treatment; in the osimertinib cohort, 56% received subsequent platinum-based chemotherapy and 35% received EGFR-TKIs, with 9% remaining on osimertinib. Twenty-one percent of SoC patients received subsequent platinum-based chemotherapy, 33% received EGFR tyrosine kinase inhibitors (TKIs), and 43% were treated with osimertinib.

With osimertinib the median time to discontinuation of study treatment or death was 20.8 months (95% CI, 17.2-24.1) compared to 11.5 months (95% CI, 10.3-12.8) with SoC. The median time to discontinuation of any EGFR-TKI or death was 23.0 months (95% CI, 19.5-not calculable [NC]) with osimertinib versus 16.0 months with SoC. In the osimertinib and SoC cohorts, 91 (67%) and 206 (74%) patients, respectively, remained on study treatment for at least 7 days following investigator-assessed progression. Median duration on study treatment post-progression in the respective cohorts was 8.1 weeks (95% CI, 6.3-12.3) versus 7.0 weeks (95% CI, 5.9-8.1)

Time-to-event post-progression endpoints all favoured osimertinib: The median time to first subsequent therapy (TFST) or death was 23.5 (95% CI, 22.0-NC) versus 13.8 months (95% CI, 12.3-15.7) in the osimertinib and SoC EGFR-TKI arms respectively, HR 0.51 (95% CI, 0.40-0.64, p < 0.0001).



Caption for image: PFS benefit with osimertinib is preserved through Time to First Subsequent Therapy.

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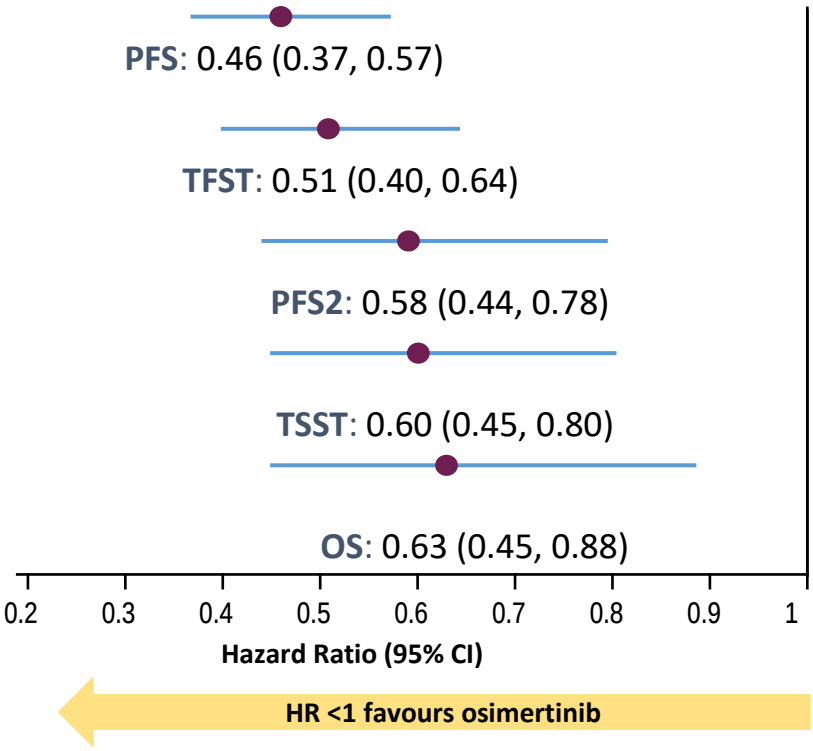
In the osimertinib versus SoC cohorts, 73 (26%) versus 106 (38%) patients experienced a second progression or died; the median PFS with subsequent therapy (PFS2) was NC (95% CI, 23.7-NC) versus 20.0 months (95% CI, 18.2-NC) respectively, HR 0.58 (95% CI, 0.44-0.78, p = 0.0004). Second subsequent therapy (SST) or death occurred in 74 (27%) osimertinib versus 110 (40%) SoC patients; of these, 24 (9%) versus 39 (14%) initiated SST, and 50 (18%) versus 71 (26%) patients died.

The median time to SST (TSST) or death was NC for the osimertinib arm versus 25.9 months (95% CI, 20.0-NC) for the SoC EGFR-TKI arm, HR 0.60 (95% CI, 0.45-0.80, p = 0.0005).



Caption for image: Step-wise increase of the statistically significant HRs provides confidence in the interim OS data.

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On 17 April 2018 the FDA granted an approval to osimertinib as a first-line treatment for patients with NSCLC whose tumours have EGFR mutations consisting of exon 19 deletions or exon 21 L858R substitution mutations based on findings of the phase III FLAURA study. NCT02296125. Planchard *et al.* Abstract128O

Practice point and future research opportunities

As a study endpoint, OS is the gold standard, unambiguous, and independent of bias-prone variables. However, it is impractical because of the length, cost, and the size of clinical trials. In terms of capturing the impact of subsequent therapies, it is both beneficial and detrimental; it does not take into account the contribution of subsequent therapies by treatment arms. The PFS is easier to measure but depends on bias-prone variables such as frequency of assessment or definition of progression. Furthermore, PFS benefit often does not translate into OS benefit. PFS2 is recommended for use when OS cannot be measured for clinical and financial reasons to assess clinical benefit of agents that do not induce responses, effect of maintenance therapy, impact of crossover on OS assessment, and whether the experimental therapy positively or negatively affects efficacy in the subsequent therapy (spill-over effect).

In FLAURA, post-progression outcome endpoints (TFST, PFS2, TSST) are more likely to be associated with OS. All post-progression outcome endpoints were prolonged with osimertinib versus SoC EGFR-TKI, providing greater confidence in the interim OS data. In addition, time to discontinuation of TKI was longer in the osimertinib arm, even with reasonable crossover from the SoC to osimertinib. These data further support the first-line use of osimertinib for EGFR-mutated NSCLC patients as one of the best treatments.

Adding local therapy to a TKI in the first-line improves survival in patients with NSCLC and oligometastatic or oligoprogressive liver metastasis

Tao Jiang and Caicun Zhou of the Medical Oncology Department of Shanghai Pulmonary Hospital, Tongji University, Shanghai, China compared progression-free survival (PFS) with local therapy plus epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) to EGFR-TKI treatment only. Their previous study demonstrated that liver metastases were a negative predictive and prognostic factor in EGFR mutated NSCLC patients treated with EGFR-TKIs, suggesting that additional treatment was warranted.

This study included 289 patients with EGFR mutated NSCLC and liver metastases; of these, 55 patients had oligometastatic liver metastases, which was defined as < 5 sites in liver without extrahepatic metastases at initial diagnosis, and 63 had oligoprogressive liver metastases, defined as < 5 sites in liver without extrahepatic metastases during TKIs therapy. Eighteen patients in the oligometastatic cohort (n=55) were treated with EGFR-TKIs and 21 patients received TKIs plus local therapy. The study's objective was progression-free survival (PFS), which was calculated from the time of initiation of TKI therapy to the first RECIST v1.1 defined disease progression (PD) or death and PFS2 was calculated from time of initiation of TKI therapy to off-TKI PD in the oligoprogressive cohort.

Of the 63 patients with oligoprogressive disease, 19 received continuation of TKIs plus local therapy and 22 received switch therapy. Median PFS was comparable in these treatment groups; however, median PFS2 was prolonged in the local therapy/TKI cohort to 13.9 months compared to 8.8 months in the switch therapy arm (p = 0.050). Median OS was also longer with local therapy plus TKI versus switch therapy at 24.7 versus 15.7 months, respectively (p = 0.085).

Median PFS was significantly longer at 12.2 months in patients with NSCLC and oligometastatic or oligoprogressive liver metastases receiving local therapy plus a TKI compared to 7.9 months in similar patients treated with only TKIs (p = 0.030). A non-significant trend toward improved overall survival (OS) favoured the local therapy/TKI cohort over the TKI arm, (31.7 versus 21.3 months, respectively; p = 0.102). Jiang *et al.* Abstract 129O

Practice point and future research opportunities

Findings from this study indicate that EGFR-TKIs plus local therapy provided a prolonged survival benefit compared with TKIs alone in the first-line setting in patients with EGFR mutated NSCLC and oligometastatic or oligoprogressive liver metastases. Median PFS was significantly improved with the addition of local therapy to an EGFR-TKI over sole treatment with a TKI in patients with EGFR mutated NSCLC and oligometastatic or oligoprogressive liver metastases. Multivariate analysis revealed that the addition of local therapy was independently associated with prolonged PFS and OS.

T-stage at diagnosis and adenocarcinoma histology may indicate a better prognosis in oligometastatic non-small-cell lung cancer

Oscar Juan, Medical Oncology, Hospital Universitari i Politècnic La Fe, Valencia, Spain explained that oligometastatic non-small cell lung cancer (NSCLC) is a distinct prognostic group within stage IV lung cancer that may show improved overall survival (OS) with ablative surgery or radiotherapy. Dr. Juan and colleagues analysed the clinical factors influencing outcome in a series of patients with oligometastatic NSCLC treated in a tertiary hospital. The study included 84 patients diagnosed with oligometastatic NSCLC, which was defined as ≤3 metastatic lesions at diagnosis, from January 2012 to December 2016. Median OS was calculated by the Kaplan-Meier method, and the association between clinical and pathological factors and OS was determined using univariate and multivariable Cox regression models; the multivariate analysis was done only on variables having a p-value <0.01 in univariate analysis.

Of the 84 patients included in the study, 25 (29.8) had squamous histology, 58 (58%) had adenocarcinoma and one (1.2%) patient had undifferentiated carcinoma. Eleven (13%) patients were epidermal growth factor receptor (EGFR) mutation positive. The majority (78.3%) of patients had one, and 20.5% of patients had two metastatic sites. Metastatic sites included the CNS (39.2%), bone (29.8%), lung (17.9%), adrenal (11.9%), and liver (10.7%). Local treatment was administered to 57 (67.9%) patients consisting of surgery in 8.8% of patients, radiotherapy in 70.2% of patients, and 21.2% of patients underwent both. Local therapy was provided prior to chemotherapy in 68.2% and during chemotherapy in 49.1% patients.

At a median follow-up of 10.5 months, the median OS was 15.8 months, 95% confidence interval (CI), 8.9-22.7. In multivariable analysis, significant associations with OS were found only for T-stage ($p = 0.012$), and adenocarcinoma histology ($p = 0.006$). On univariate analysis, sex, smoking, and N-stage did not significantly associate with OS (all $p > 0.01$). Juan *et al.* Abstract 137PD

Practice point and future research opportunities

In this series, ablative therapy in oligometastatic NSCLC patients did not associate with improved OS. The only factors that did associate significantly with OS were a lower initial T-stage in the primary tumour and adenocarcinoma histology, which may indicate a more

favourable prognosis. The optimal management of oligometastatic NSCLC patients will require robust data from well-designed prospective clinical trials.

Real-world data of PD-L1 expression in locally advanced or metastatic NSCLC shows similar prevalence as that reported in clinical trial screening population

Manfred Dietel, Institute of Pathology, Charite Berlin Mitte, Berlin, Germany, presented real-world data from the EXPRESS study on the prevalence of PD-L1 expression on tumour cells. This global, multicentre, retrospective observational study included patients 18 years and older with histologically confirmed stage IIIB/IV advanced non-small cell lung cancer (NSCLC) and a tumour tissue block that was 5 years old or less. The tissue had been obtained before treatment at or after this stage was determined. Immunohistochemistry was used to assess PD L1 tumour expression using the 22C3 pharmDx kit in 45 centres across 18 countries. The percentages of patients with PD-L1 tumour proportion scores (TPS) ≥50%, TPS ≥1%, and TPS <1% were described overall and by relevant clinicopathological characteristics.

Of 2634 patients meeting the inclusion criteria, 2435 (92%) had PD-L1 data. Most (1977) patients were younger than 75 years and 457 patients were 75 years and older; 925 patients were female.

TPS ≥50% was determined in 540 (22%) patients, while 1256 (52%) were TPS ≥1%, and 1179 (48%) were TPS <1%. TPS ≥50% occurred in approximately 22.2% in all patients regardless of age, gender and primary and metastatic tumours. Never, former, and current smoking status was reported for 553, 660, and 762 patients, respectively; TPS ≥50% was highest in former (24.1%) and current smokers (24.5%) compared to never smokers (18.1%)

PD-L1 TPS levels varied slightly according to geographic location. The percentages of patients with PD-L1 TPS ≥50% were 22% in Europe, 22% in Asia Pacific, 22% in the Americas, and 24% in other countries, whereas PD-L1 TPS ≥1% was reported at 51% in Europe, 53% in Asia Pacific, 47% in the Americas, and at 54% in other countries. Dietel *et al.* Abstract 130O

Practice point and future research opportunities

This is the largest real-world study in advanced NSCLC to date evaluating PD-L1 tumour expression using the 22C3 pharmDx kit. Even though evaluation of PD-L1 TPS was performed locally across a large number of sites, the testing failure rate was low. Prevalence of PD-L1 TPS ≥50% and TPS ≥1% was similar across geographic regions and broadly consistent with central testing results from screening done in clinical trial populations (Aggarwal *et al.* Ann Oncol 2016; 27:1060P).

Frontline atezolizumab combination emerges as a potential new standard in NSCLC

Lead investigator Martin Reck, Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Grosshansdorf, Germany presented findings from the phase III IMpower150 trial comparing atezolizumab added to bevacizumab plus chemotherapy with bevacizumab plus chemotherapy for patients with advanced non-squamous non-small cell lung cancer (NSCLC). Prof. Reck explained the rationale for these combinations was that atezolizumab's T-cell mediated cancer cell killing may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression, while the chemotherapy of carboplatin plus paclitaxel may induce immune responses.

The anti–PD-L1 agent atezolizumab is currently approved in the United States and the European Union for the treatment of NSCLC regardless of PD-L1 expression in the second line and beyond.

IMpower150 randomised 1202 patients with stage IV non-squamous NSCLC cancer in a 1:1:1 ratio to receive atezolizumab with carboplatin and paclitaxel chemotherapy (arm A), atezolizumab with carboplatin/paclitaxel plus bevacizumab (arm B), or carboplatin/paclitaxel plus bevacizumab (arm C). Atezolizumab was administered at 1200 mg i.v. every 3 weeks and bevacizumab was given at 15 mg/kg. Patients in each arm received carboplatin and paclitaxel on day 1 of each cycle for 4 to 6 cycles. Maintenance therapy was administered in arm A with atezolizumab alone, and in arm B, patients received bevacizumab plus atezolizumab. Patients in arm C received maintenance therapy consisting of bevacizumab alone. For the patients in arms B and C, 61% (n = 356) and 62% (n = 336) were men and the ECOG performance status was 0 for 39% and 43%, respectively. Overall, the median age of the patients was 63 years and 60% were previous smokers. The minimum and median follow-up was 9.5 and approximately 15 months, respectively for the interim analysis, which was designed to compare arms B and C.

The atezolizumab combination delayed progression or death by 38% compared with bevacizumab/chemotherapy. The median progression-free survival (PFS; co-primary endpoint) was 8.3 months versus 6.8 months, in arm B versus arm C, respectively (hazard ratio [HR] 0.62; 95% confidence interval [CI], 0.52-0.74; $p < 0.0001$). The 6-month and 12-month PFS rates were 67% (95% CI, 0.22-0.72) versus 56% (95% CI, 0.51-0.62), and 37% (95% CI, 0.31-0.42) versus 18% (95% CI, 0.13-0.23) in arm B versus arm C, respectively. The objective response rate (ORR) for the atezolizumab arm was 64%, comprising a 4% complete response (CR) rate and 60% partial response (PR) rate. Among patients receiving bevacizumab plus chemotherapy alone, the ORR was 48%, comprising 1% CR and 47% PR. In the respective cohorts, the median duration of response was 9.0 months (range, 0.4 to 24.9) and 5.7 months (range, 0.0 to 22.1).

The investigators also evaluated the T-effector (Teff) gene signature expression, as defined by mRNA expression of 3 genes (PD-L1, CXCL9, and IFNγ) as well as PD-L1 levels by immunohistochemistry: Teff was detected in 177 (44%) arm B and 166 (42%) arm C patients.

The trial met the second co-primary endpoint of PFS in the Teff-high cohort, which demonstrated a landmark median PFS of 11.3 months (95% CI, 9.1-13.0) with the atezolizumab combination, compared to 6.8 months (95% CI, 5.9-7.4) with bevacizumab/chemotherapy (HR, 0.505; 95% CI, 0.377-0.676; p < 0.0001). In this subgroup, 6- and 12- month PFS rates were 72% and 46% with the atezolizumab combination versus 57% and 18% with chemotherapy/bevacizumab. Patients with high Teff gene expression and wild-type EGFR in the atezolizumab cohort demonstrated an ORR of 69%, comprising a 4% CR rate and 65% PR rate, compared to a 54% ORR rate, comprising a 2% CR rate and 51% PR rate with chemotherapy plus bevacizumab. The median duration of response was 11.2 months (range, 0.5 to 24.9) and 5.7 months (range, 0 to 22.1) months, respectively.

PD-L1 expression levels were comparable between arms B and C. In patients with high PD-L1 (TC3/IC3), the median PFS was 12.6 versus 6.8 months (HR, 0.39) in the atezolizumab group versus the chemotherapy/bevacizumab arm. In addition, patients testing negative (TC0/IC0) for PD-L1 showed an improvement in PFS with atezolizumab (median PFS, 7.1 versus 6.9 months; HR, 0.77). In another subgroup of patients with a biomarker of interest, patients with EGFR or ALK mutations demonstrated a median PFS of 9.7 versus 6.1 months with the respective treatments. Additionally, in the ITT EGFR wild-type population, investigator-assessed median PFS was 8.3 months (95% CI, 7.7- 9.8) with the atezolizumab combination compared to 6.8 months (95% CI, 6.0-7.1) with bevacizumab and chemotherapy alone (HR, 0.617; 95% CI, 0.517-0.737; p < 0.0001). The incidence of serious adverse events (AEs) and immunological AEs, was similar between treatment arms. NCT02366143. Reck *et al.* Abstract 134PD

Practice point and future research opportunities

The combination of atezolizumab bevacizumab carboplatin, and paclitaxel has emerged as a potential new standard of care for the treatment of patients with metastatic non-squamous NSCLC in the first-line setting. IMpower150 is the first phase III immunotherapy-based combination study to demonstrate a statistically significant and clinically meaningful improvement in PFS and response rates in an all-comer first-line metastatic non-squamous NSCLC setting.

Patients with NSCLC demonstrate durable response with atezolizumab in the phase III POPLAR trial

Julien Mazières, Thoracic Oncology, Toulouse University Hospital, Toulouse, France and colleagues conducted the POPLAR trial, which enrolled 287 patients with previously treated non-small cell lung cancer (NSCLC) who were randomised to receive atezolizumab monotherapy at 1200 mg (n=144) or 75 mg/m2 of docetaxel (n=144) by i.v. every 3 weeks. PD-L1 expression was also assessed on tumour cells (TC) and tumour-infiltrating immune cells (IC) using the VENTANA SP142 immunohistochemistry assay.

Analysis done after a minimum follow-up of 3 years revealed patients in the overall trial population and patients with PD-L1 positive tumours had significantly improved survival with atezolizumab compared to docetaxel chemotherapy. The 2- and 3- year overall survival (OS)

rates in the intent to treat population with atezolizumab versus docetaxel were 32.2% versus 16.6% (p = 0.0027) and 18.7% versus 10.0%, respectively (p = 0.0419). While the objective response rate (ORR) in this population was 15% with both treatments, the median duration of response was 3-fold longer with atezolizumab at 22.3 months (95% confidence interval [CI], 11.6-31.1) versus 7.2 months (95% CI, 5.8-12.2) with docetaxel.

The OS improved as the levels of PD-L1 expression increased. In patients with the highest expression levels, TC3 or IC3, the 2-year and 3-year OS rates with atezolizumab versus docetaxel were 41.7% versus 19.9% (p = 0.1003) and 37.5% versus 14.9% (p = 0.0724), respectively. Patients with PD-L1 expression TC2/3 or IC2/3 had 2- and 3-year OS rates of 36.1% versus 13.8% (p = 0.0082) and 21.2% versus 9.9% (p = 0.1168) with atezolizumab versus docetaxel, respectively. Patients with PD-L1–negative tumours (TC0 and IC0) also showed improved 2-and 3-year OS rates of 25.0% versus 6.8% (p = 0.0202) and 20.5% versus 6.8% (p = 0.0693) with atezolizumab versus docetaxel, respectively.

Improved OS rates with atezolizumab compared to docetaxel were also consistent across squamous and non-squamous tumour histology. The respective 2- and 3-year OS rates with atezolizumab versus docetaxel were 32.2% versus 21.1% (p = 0.960) and 23.3% versus 12.4% (p = 0.0585) for non-squamous histology and 32.7% versus 7.8% (p = 0.0020) and 9.4% versus 5.2% (p = 0.4603) for squamous histology.

Additionally, fewer grades 3 to 5 adverse events were reported in patients treated with atezolizumab compared to docetaxel chemotherapy. NCT01903993. Mazieres *et al.* Abstract 135PD

Practice point and future research opportunities

Atezolizumab is a selective humanised monoclonal IgG1 antibody against PD-L1. The 3-year survival analysis of the POPLAR study describes the longest survival follow-up reported to date of an all-comer randomised PD-L1/PD-1 immunotherapy trial in the second-line and beyond setting in NSCLC.

This places atezolizumab among the drugs with the highest landmark OS in previously treated lung cancer patients. The fact that all subgroups of patients benefitted to a similar degree is a double-edged sword: It is good in the sense that atezolizumab can be tried in all advanced NSCLC patients; however, this also means that we cannot predict which patients are most likely to live for 3 years. Biomarkers are needed to help identify the long-term survivors.

Health-related QoL data support alectinib as first-line standard of care in ALK-positive NSCLC

Maurice Pérol, Thoracic Oncology, Centre Léon Bérard, Lyon, France discussed previously reported results from the phase III ALEX trial, which compared the next-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) alectinib with the standard of care, crizotinib, in the first-line that revealed alectinib had superior efficacy over crizotinib, (hazard ratio [HR] 0.47 for disease progression or death; 95% confidence interval [CI], 0.34-0.65; $p < 0.001$. In ALEX, 303 patients with ALK-positive non-small cell lung cancer (NSCLC) were randomised 1:1 to receive alectinib at 600 mg or crizotinib at 250 mg twice daily.

Dr. Pérol then presented findings from patient-reported outcomes (PROs) of health-related quality of life (QoL) completed by the patients in ALEX, specifically the EORTC QLQ-C30 questionnaire, which was used to evaluate health-related QoL, and the EORTC QLQ-LC13 questionnaire, which assessed lung cancer-related symptoms. The questionnaires were assessed at baseline, every 4 weeks during treatment, within the 4 weeks after study withdrawal, and after disease progression. Both questionnaires were completed by 66% and 64% of patients in the alectinib and crizotinib groups, respectively.

Health-related QoL, which was defined as the time to deterioration, in patients treated with alectinib was 88 weeks compared to 68 weeks with crizotinib. Both treatment arms showed clinically meaningful improvement in lung cancer symptoms; however, the duration of improvement was longer with alectinib compared to crizotinib. Improvement with alectinib versus crizotinib in cough was 96 versus 84 weeks, chest pain was 96 versus 80 weeks, fatigue was 96 versus 68 weeks, and pain in other parts was 96 versus 68 weeks, respectively.

The patient reported outcomes (PRO) data were consistent with the main results of the trial wherein the primary analysis showed a similar response rate for crizotinib and alectinib, but a longer duration of response with alectinib. Furthermore, fewer patients on alectinib reported a clinically meaningful worsening in treatment-related symptoms such as diarrhoea, peripheral neuropathy, constipation, dysphagia, appetite loss, and nausea/vomiting.

In a subgroup of patients having CNS metastases at baseline, 10.8% of patients treated with alectinib reported worsening health-related QoL starting at week 4 compared to 20.6% of patients on crizotinib. This assessment held through week 84, with 0% of alectinib and 16.7% of crizotinib patients reporting worsening health-related QoL. Nearly half as many patients with CNS metastases at baseline on alectinib reported declines in cognitive function at week 32; 17.9% of alectinib compared to 34.6% of crizotinib treated patients reported worsening cognitive function.

Alectinib also demonstrated a superior tolerability profile compared to crizotinib shown in the PRO data that was consistent with the adverse events profile recorded during the study. BO28984. Perol *et al.* Abstract 138PD

Practice point and future research opportunities

The PRO data in the ALEX trial support the use of alectinib as a new standard of care in the frontline treatment of patients with ALK-positive lung cancer. The duration of symptom improvement was longer with alectinib than with crizotinib treatment in these patients. Additionally, the high level of CNS activity shown with alectinib in the primary analysis is consistent with the fact that fewer patients treated with alectinib reported clinically meaningful worsening in health-related QoL or cognitive function compared to crizotinib.

Patients with EGFR-mutated NSCLC report clinically relevant improvement in cough with osimertinib treatment

Natasha Leighl, Medical Oncology Department, Princess Margaret Hospital, Toronto, Canada presented quality of life (QoL) data on behalf of colleagues that derived from patient reported outcomes (PROs) on two widely used QoL questionnaires. These QoL data came from patients participating in the phase III FLAURA trial wherein 248 patients were randomised to osimertinib and 252 patients to standard of care (SoC) comprising an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Efficacy findings from the FLAURA trial have already been published that demonstrated patients on osimertinib had significantly longer progression-free survival (PFS) hazard ratio [HR] 0.46; 95% confidence interval [CI], 0.37-0.57 ($p < 0.001$) and improved overall survival (OS) compared to patients on SoC (HR 0.63, 95% CI, 0.45-0.88; $p = 0.007$). (Soria JC *et al. N Engl J Med* doi: 10.1056/NEJMoa1713137).

More than 60% of patients in both treatment cohorts completed QoL questionnaires at all time points, including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC-QLQ-C30) at baseline and every 6 weeks thereafter, and the Lung Cancer 13 items (QLQ-LC13) at baseline, then weekly for 6 weeks followed by every 3 weeks. Scoring ranges from 0 to 100 with higher scores representing greater symptom burden and a difference ≥10-points was considered clinically relevant. The pre-specified key symptoms included cough, dyspnoea, chest pain, fatigue, and appetite loss. The mean baseline scores were equivalent in the osimertinib and SoC arms for the key symptoms: cough (32.8 versus 33.5), dyspnoea (22.5 versus 25.0), chest pain (19.5 versus 20.8), appetite loss (22.7 versus 25.6) and fatigue (32.2 versus 35.8).

The PROs revealed that key symptoms improved in both treatment arms from baseline until randomised treatment discontinuation; however, this was clinically relevant only for cough in the osimertinib arm (-10.14). Change in cough for SoC was -8.18. Changes from baseline in other key symptoms with osimertinib versus SoC, respectively, included chest pain (-6.8 versus -3.9), appetite loss (-5.8 versus -4.4), fatigue (-3.3 versus -3.3), and dyspnoea (-3.2 versus -1.2). With the exception of chest pain ($p = 0.021$), there were no significant differences between the osimertinib and SoC arms.

Symptom	Treatment	Adjusted mean (95% CI)	Estimated treatment difference[b] (95% CI)	*p* value
Cough	Osimertinib	**–10.14** (–12.12, –8.16)	–1.96 (–4.83, 0.91)	0.180
	SoC	–8.18 (–10.25, –6.10)		
Dyspnoea	Osimertinib	–3.19 (–4.92, –1.47)	–1.99 (–4.45, 0.47)	0.113
	SoC	–1.20 (–2.95, 0.54)		
Chest pain	Osimertinib	–6.84 (–8.58, –5.10)	–2.96 (–5.47, –0.45)	0.021
	SoC	–3.88 (–5.69, –2.07)		
Fatigue	Osimertinib	–3.30 (–5.45, –1.16)	0.01 (–3.22, 3.25)	0.993
	SoC	–3.32 (–5.68, –0.95)		
Appetite loss	Osimertinib	–5.81 (–8.24, –3.39)	–1.46 (–5.08, 2.15)	0.427
	SoC	–4.35 (–7.04, –1.66)		

[a]Treatment, visit and treatment by visit interaction were fitted as fixed effects in the model; patient fitted as a random effect. Compound symmetry was used as the covariance structure for all models.
[b]Osimertinib minus SoC.
CI, confidence interval; MMRM, mixed-effects model for repeated measures; SoC, standard of care.

Caption for image: Key symptoms improved in both treatment arms from baseline until randomised treatment discontinuation; however, this was clinically relevant only for cough in the osimertinib arm.

© Natasha Leighl.

All changes from baseline in other key symptoms, excepting fatigue, favoured osimertinib versus SoC, including chest pain (AMC -6.8 versus -3.9), appetite loss (AMC -5.8 versus -4.4), and dyspnoea (AMC -3.2 versus -1.2). The changes from baseline regarding fatigue were equal in the treatment arms (AMC -3.3 versus -3.3). With the exception of chest pain (p = 0.021), there were no statistically significant differences between the osimertinib and SoC arms. Improved QLQ-C30 functional and global health/QoL scores were also reported that showed no clinically relevant differences between cohorts. NCT02296125. Leighl *et al.* Abstract 139PD

Practice point and future research opportunities

Compliance was above 70% at most of the time points in both treatment arms: at baseline for QLQ-LC13, 90.8% in osimertinib arm and 92.0% in SoC arm and for QLQ-C30, 95.2% in osimertinib arm and 94.1% in SoC arm. Key patient-reported symptoms have been improved in both treatment arms from baseline until randomised treatment discontinuation; however, it was clinically relevant only for cough in osimertinib arm. The degree of change perceived to be clinically significant could well differ from population to population and from patient to patient.

Minor benefits for osimertinib were observed in term of chest pain, emotional, cognitive and social functioning. Time to deterioration of key symptoms was similar between treatment arms.

It is very important to study PROs, especially for TKIs, as longer treatment periods and daily dosing potentially burden the patients with drug-related adverse events. More research is needed on patients' experiences captured with standardised measures, integration and report alongside more traditional trial outcome. In practice, regular assessment of PROs would permit more timely, supportive interventions to reduce symptoms and side effects. It is important to encourage reporting PROs alongside PFS and other more traditional outcomes, not published in a separate paper.

Patient outcome is not improved by necitumumab in combination with abemaciclib in stage IV NSCLC

Benjamin Besse, Department of Medicine, Institut Gustave Roussy, Villejuif, France presented findings from a 2-part, single-arm study with an expansion cohort that was designed to evaluate the safety and efficacy of necitumumab in combination with abemaciclib in comparison with historical data. The trial was initiated to determine the dose-limiting toxicity (DLT) of abemaciclib administered twice daily at doses ranging from 100 mg to 200 mg when combined with necitumumab in patients with stage IV non-small cell lung cancer (NSCLC). The optimal dose was determined by the number of patients having a DLT in the first cycle of treatment. Necitumumab was delivered at a standard 800 mg on days 1 and 8 of a 21-day cycle. The primary endpoint of the trial was progression-free survival (PFS) at 3 months.

The study enrolled 66 patients with a median age of 61 years (range, 37 to 85); 26 patients (39.4%) were aged 65 years or older. Forty-seven of the patients were male, and 83.3% of patients were current or former smokers. Histology was non-squamous stage IV NSCLC in 35 patients and 27 had squamous histology. The second part of the study was a dose extension with 50 patients added; 25 patients each with non-squamous and squamous NSCLC.

Median PFS was 2.14 months, 95% confidence interval (CI), 1.41-2.76, and median overall survival (OS) was 6.93 months, 95% CI, 4.96-12.85. The PFS rates at 3 and 6 months were 32.3% and 22.2%, respectively. OS at 6 months was 57.3%.

Maximum tolerated dose was determined in cycle 1 for necitumumab at 800 mg and abemaciclib at 150 mg, with 57 patients receiving this regimen. During the dose experimentation phase, 3 patients developed a DLT in cycle 1. One patient assigned to 150 mg of abemaciclib experienced grade 3 diarrhoea. In the cohort receiving 200 mg of abemaciclib there was 1 case of grade 3 stomatitis and 1 case of grade 4 thrombocytopenia. No new clinically significant safety concerns emerged from this study, and the safety profile of necitumumab and abemaciclib in combination was consistent with the safety profiles of the individual study drugs. Treatment-related adverse events (TRAEs) occurred in 20% of patients. Grade ≥3 TRAEs included fatigue in 8 patients, diarrhoea in 4, decreased appetite in 4, dyspnoea in 5, vomiting in 4, and hypokalemia occurred in 4 patients. NCT02411591. Besse *et al.* Abstract 134PD

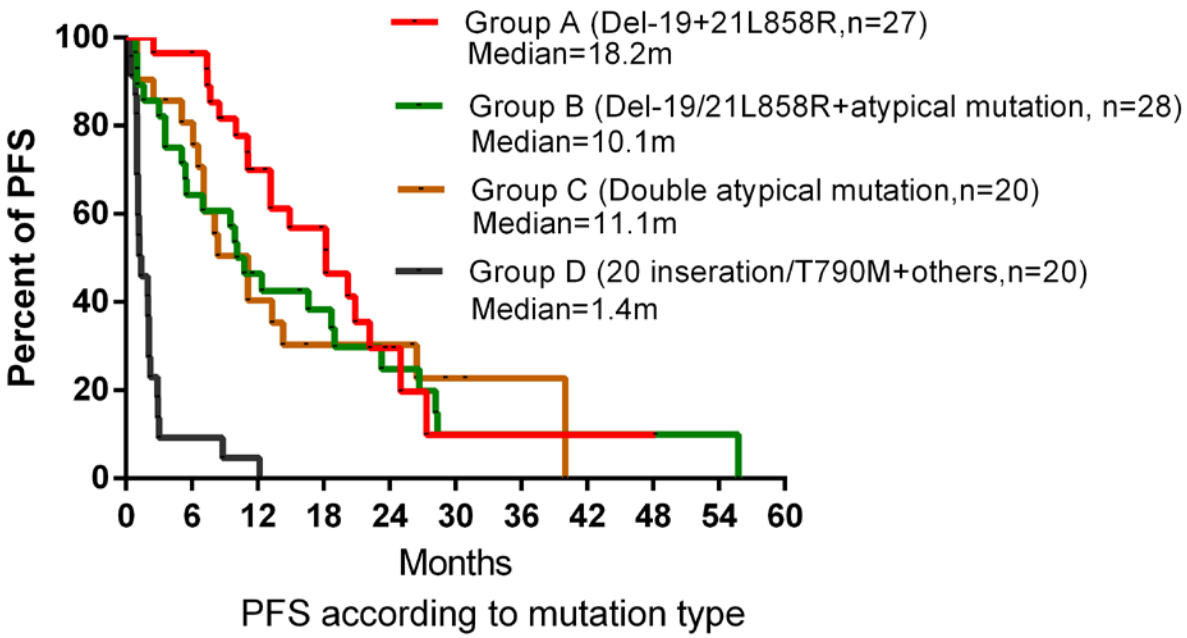
Practice point and future research opportunities

This phase Ib study of necitumumab in combination with abemaciclib failed to meaningfully improve outcomes in patients with stage IV NSCLC. The challenge in stage IV NSCLC remains in finding effective third-line treatment. Currently the third-line approved agent is erlotinib, which has poor activity in an unselected population. This combination was tested because necitumumab, which targets the EGFR, is approved for first-line treatment in combination with cisplatin and gemcitabine in squamous lung cancer patients. The CDK4/6 inhibitor, abemaciclib, has a totally different mechanism; thus, a biological rationale exists for combining these drugs.

Tyrosine kinase inhibitor treatment provides different response rates in patients with advanced lung adenocarcinoma and complex EGFR mutations

Baihua Zhang, Pulmonary Department, Shanghai Chest Hospital, Shanghai, China explained that patients with advanced lung adenocarcinomas often harbour complex mutations, such as two or more different epidermal growth factor receptor (EGFR) mutations within a single tumour sample. Whether the presence of complex mutations altered the efficacy of standard first-line treatment with tyrosine kinase inhibitors (TKIs) was unknown. In addition, the frequency of complex mutations was also undocumented prompting Dr. Zhang and collegues to conduct this retrospective analysis of data from consecutive patients diagnosed with lung adenocarcinoma and an EGFR mutation from January 2011 to January 2017. The investigators reviewed the efficacy of TKI treatment in patients with complex mutations; of the 16,840 subjects that underwent screening, 5898 patients were positive for EGFR mutations.

Complex mutations were diagnosed in 187 patients for a frequency of 3.2% in the EGFR mutant patients. Of these patients, 95 had advanced lung adenocarcinoma and were treated with TKIs. While the 27 patients with adenocarcinoma and Del-19+21L858R mutation demonstrated an objective response rate (ORR) of 72.7% with TKI treatment, 28 patients with Del-19/21L858R+ atypical mutations had an ORR of just 54.2% and 20 patients with double atypical mutations had an ORR of 66.7% following TKI treatment. Median progression free survival (PFS) in the respective cohorts was 18.2 months (95% confidence interval [CI], 12.0-24.4), 10.1 months (95% CI, 6.5-13.7), and 11.1 months (95% CI, 6.8-15.4). The poorest response was seen in 20 patients with tumours harbouring complex mutations with a primary drug-resistant pattern who demonstrated an ORR of 15.0% with TKI treatment. Median PFS in these patients was just 1.4 (95% CI, 0.2-2.5) months.



Caption for image: PFS according to mutation type.

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Zhang *et al.* Abstract 140PD

Practice point and future research opportunities

Complex EGFR mutations account for 3.2% of the entire EGFR mutation spectrum. Patients with double classical mutations had the best PFS compared with other mutation types and may benefit more from TKI treatment. Those who harboured complex mutations with classical pattern or double atypical mutations derived similar PFS compared with individuals who had single classical mutation.

Real world study of molecular testing status in EGFR mutation-positive NSCLC patients with disease progression during EGFR TKI treatment

Kuninobu Kanai, Wakayama Medical University Hospital, Wakayama, Japan presented findings from the multicentre, prospective, observational REMEDY study of molecular testing status in patients with EGFR mutated non–small cell lung cancer (NSCLC) and explained that approximately 50 to 60% of the patients will acquire resistance by the T790M mutation, making EGFR tyrosine kinase inhibitors (EGFR TKI) treatment ineffective. The third generation EGFR TKI osimertinib is a standard of care for patients with tumours harbouring T790M mutations but eligibility in Japan for osimertinib therapy is dependent upon determining the mutation status

using a validated diagnostic test based on tumour tissue or a plasma. To lessen the risk of false negatives, the Japan Lung Cancer Society's guidance on the EGFR mutation test recommends using tissue sample over plasma sample and to retest T790M negative samples as determined by prior tests done using plasma test on a tissue sample. Therefore, the investigators conducted this study to investigate the real world practice of sample collection and T790M testing in Japan.

This study included patients diagnosed with EGFR mutation-positive advanced NSCLC who progressed on EGFR-TKI treatment. The primary endpoints were the sample collection rate for EGFR T790M mutation test at disease progression, the rate of EGFR T790M gene mutation testing, and the EGFR T790M detection rate.

Findings from an interim analysis of 111 patients showed that sample collection was done in 104 (93.7%) patients that consisted of a tissue sample in 19 patients, cytology samples in 14 patients, and plasma samples from the remaining 71 patients. An EGFR T790M mutation test was conducted in 103 (92.8%) patients that yielding a T790M mutation detection rate in 16 patients with adequate tissue samples of 43.8% that was higher than the T790M mutation detection rates of 21.4% with cytology; 61% of the 71 patients tested by plasma were circulating tumour DNA 'non-shedders' who showed no detectable EGFR mutation. UMIN ID; 000024928. Zhang *et al.* Abstract 141PD

Practice point and future research opportunities

Tissue samples are the gold standard for detection of EGFR T790M mutation, with cytology also showing better detection levels than plasma. The rates of EGFR T790M mutation testing following disease progression on a TKI were high but could be improved.

Detection of EGFR mutations in cerebrospinal fluid of EGFR mutated lung adenocarcinoma with brain metastases

Liang Shi, Department of Medical Oncology, Beijing Chest Hospital, Beijing, China underscored the difficulty in obtaining brain metastasis biopsy making it hard to study the resistance mechanisms of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with lung adenocarcinoma and brain metastases. Dr. Shi and colleagues investigated the alternative detection of EGFR mutation status in intracranial lesions by liquid biopsy of cerebrospinal fluid (CSF).

The study included 30 patients treated for lung adenocarcinoma with brain metastasis and primary tumours harbouring activating EGFR mutation, as determined by the amplification-refractory mutation system (ARMS) assay from July 2014 to June 2017 in the Beijing Chest Hospital. Matched CSF and plasma samples were obtained and droplet digital PCR assays for EGFR mutations, including 19del, L858R, and T790M were performed using two millilitres of CSF or plasma. The study objectives were the intracranial objective response rate (iRR), intracranial progression-free survival (iPFS), and intracranial overall survival (iOS) from the time of diagnosis of brain metastasis. All 30 study patients were Chinese that had been diagnosed with stage IV lung adenocarcinoma. Twenty-one patients were female with a median age of 59

years (range, 34 to 75 years) and 24 patients were classified as good ECOG performance status < 2.

CSF cytology testing was negative for EGFR mutations in all patients and examinations of cranial imaging showed no leptomeningeal metastases. In PCR assays, EGFR mutations were detected in the CSF of 10 (33.3%) patients, including three cases with EGFR T790M mutations, and in the plasma of 14 (46.7%) patients, which included 6 cases with EGFR T790M mutations. All EGFR T790M mutations were detected during or after treatment with an EGFR-TKIs.

Intracranial partial response (iPR) was achieved by 5 patients with activating EGFR mutations detected in CSF following treatment with combination of first-generation EGFR-TKIs and whole brain radiotherapy or stereotactic radiosurgery. The iPR was also observed in 3 patients with EGFR T790M mutations in CSF after receiving second-line osimertinib. The median iOS from the time of diagnosis of brain metastasis was 15.0 months and iPFS was 11.0 months. The EGFR testing results revealed 18 – 19del mutations and 12 L858R mutations in primary tissue; in CSR most EGFR was wild-type with plasma samples showing higher mutation frequencies. Shi *et al.* Abstract 142PD

Practice point and future research opportunities

This study shows that it is feasible to test for EGFR mutation in CSF and plasma and that CSF may serve as medium for liquid biopsy in patients with advanced lung adenocarcinoma with brain metastasis by detecting cell-free DNA within CSF to characterise EGFR mutations. For patients with advanced lung adenocarcinoma and brain metastasis harbouring EGFR mutation, dynamic monitoring of EGFR mutation status in CSF may be an appropriate choice.

Afatinib treatment results in low rates of *de novo* brain metastasis in NSCLC

James Chih-Hsin Yang, National Taiwan University Hospital and National Taiwan University Cancer Centre, Taipei, Taiwan presented findings from an analysis of pooled data of patients with and without brain metastasis at baseline treated with afatinib in the phase III LUX-Lung 3, 6 and 7 trials. Previously reported findings from these trials demonstrated improved progression-free survival (PFS) with afatinib in patients with brain metastasis compared to chemotherapy or gefitinib that was similar to the PFS observed in patients without brain metastasis (hazard ratio [HR] 0.54, 0.47, and 0.76 in LUX-Lung 3, 6 and 7, respectively). (Schuler *et al.* J Thorac Oncol 2016; 11:380–90). The PFS was also significantly improved with afatinib compared to chemotherapy in a combined analysis of LUX-Lung 3 and 6 data of patients with asymptomatic brain metastasis (HR 0.50; p = 0.0297). (Park *et al.* Lancet Oncol 2016; 17:577–89).

These findings suggested that afatinib delays the onset and/or progression of brain metastasis, prompting this analysis, which investigated whether afatinib treatment can prevent CNS progression or metastasis using competing risk analyses for the progression and metastasis pattern in the CNS or non-CNS region. The patients had stage IIIB/IV epidermal growth factor receptor (EGFR) mutation positive non-small cell lung cancer (NSCLC) and were treated with afatinib at 40 mg per day.

After median follow-up of 10.3 months, 31.3% of 48 patients with baseline brain metastasis receiving afatinib showed CNS progression compared to 52.1% of patients showing non-CNS progression, yielding a cumulative incidence at 6 and 12 months of 15.5% versus 17.7%, and 24.5% versus 24.4% of CNS versus non-CNS progression, respectively. With median follow-up of 13.0 months, 485 patients without baseline brain metastasis on afatinib had a cumulative incidence of CNS versus non-CNS progression at 6 and 12 months of 1.3% versus 17.2%, and 2.6% versus 41.2%, respectively. The risk of *de novo* CNS progression was very low at 6.4% in these patients compared with 78.4% of patients showing non-CNS progression. NCT00949650, NCT01121393, NCT01466660. Yang *et al.* Abstract 143PD.

Practice point and future research opportunities

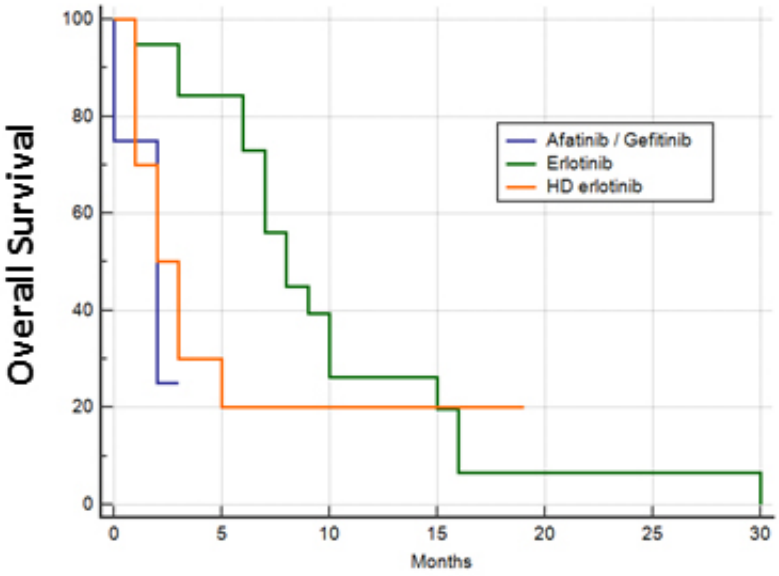
Competing risk analyses using data from LUXLung 3, 6 and 7 add to the body of evidence supporting the use of afatinib in patients with EGFR mutated NSCLC and CNS metastases. Patients with NSCLC and EGFR mutated tumours with and without brain metastasis at baseline demonstrated significantly lower incidence of CNS disease progression as compared to non-CNS metastasis after treatment with afatinib. These results suggest afatinib delays the onset/progression of brain metastasis and further support afatinib as a clinically relevant first-line treatment option for patients with EGFR mutated NSCLC and CNS metastases.

Patients with leptomeningeal metastasis and EGFR mutations benefit from second-line TKI treatment

Ronan Flippot, Medical Oncology, Gustave Roussy, Villejuif, France and colleagues conducted this retrospective study in 66 consecutive patients having epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC) who experienced leptomeningeal metastasis (LM) progression during first-line EGFR tyrosine kinase inhibitor (TKI) treatment at the Institute Gustave Roussy and Lille University Hospital from April 2003 to September 2016. The LM progression was defined as a diagnosis of LM made during TKI treatment or progression of known LM after first-line TKI. The investigators assessed overall survival (OS), progression-free survival (PFS), clinical response rate (CRR), and disease control rate (DCR) following second-line treatment using the patients´ clinical and pathological data. The DCR was defined as clinical response or stable disease lasting > 2 months. The median age of the patients was 54 (range 26 to 79) years, 51 (77%) patients were female, and 56 (85%) were non-smokers. The patients had received a median of 2 (range 1 to 7) previous lines of treatment and 19 (29%) patients had also received intrathecal treatment. Genetic analysis revealed that 23 (35%) of the patients´ tumours had exon 19 deletion, 23 (35%) tumours harboured L858R exon 21 mutation, and 10 (15%) tumours showed T790M mutation.

Second-line TKIs had been administered to 36 (55%) patients after LM progression; of these, treatment comprised erlotinib in 19 (53%) patients, 10 (28%) were treated with high dose erlotinib at 300 mg daily, 3 patients received osimertinib, and 4 patients received other first- or second-generation TKIs. The patients treated with second-line TKI, demonstrated median PFS from the time of LM progression of 3 months (95% confidence interval [CI], 2-3) and median OS was 7 months (95% CI, 3-10). The CRR was 43% and the DCR was 77%.

The median OS was 8 months (95% CI, 7-10) with second-line erlotinib, 2 months (95% CI, 1-5) with high dose erlotinib, and 2 months (95% CI, 0-2) in patients treated with other first- or second-generation TKIs. Patients treated with second-line erlotinib had been mostly pre-treated with afatinib or gefitinib (79%), and had better OS compared to patients treated with other first- or second-generation TKI after LM progression (hazard ratio [HR] 0.28; p = 0.0237). Prolonged survival was also reported with osimertinib in 3 patients harbouring T790M mutation, in which the median OS was NR (95% CI, 6-NR).



2nd line TKI	N	Median PFS (months)	95% CI	Median OS (months)	95% CI
All patients	36	3	2-3	7	3-10
Erlotinib	19	3	2-4	8	7-10
HD Erlotinib	10	1	1-3	2	1-5
Gefitinib or Afatinib	4	1	0-3	2	0-2
Osimertinib	3	6	3-NR	NR	6-NR

Caption for image: Survival of patients with NSCLC who received second-line EGFR-TKI after leptomeningeal progression.

© Ronan Flippot.

Of the 9 (25%) patients were alive at 10 months, 6 had received erlotinib, one had been treated with high dose erlotinib, and 2 patients received osimertinib. Eighty percent of patients receiving high dose erlotinib had received prior erlotinib as first-line and demonstrated a CRR of 40% and DCR of 60%. Flippot *et al.* Abstract 144PD

Practice point and future research opportunities

These data are very interesting. In general, only a little prospective randomised data are available for EGFR TKIs in CNS disease. Care of these patients should be individualised within a multidisciplinary approach. The choice of treatment should be driven by symptoms and/or the extent of CNS disease, treatment line, site(s) of progression, drug delivery to CNS, and the molecular profile of tumour.

Higher plasma concentrations of pemetrexed associate with more chemotherapy-related adverse-events in patients with advanced NSCLC

Sabine Visser, Pulmonary Medicine, Erasmus University Medical Centre, Rotterdam, Netherlands presented findings from a prospective observational multicentre study using population pharmacokinetic (PK) modelling to investigate the predictive ability of total exposure to pemetrexed for progression-free survival (PFS) and overall survival (OS) and for the occurrence of severe chemotherapy-related adverse events (AEs) in non-small cell lung cancer (NSCLC). The study enrolled patients with stage IIIB/IV NSCLC receiving first- or second-line pemetrexed/platinum. Pemetrexed was administered at 500 mg/m2 as a 10-min intravenous infusion every 21 days. Plasma samples were taken before pemetrexed and each week after infusion. For pharmacokinetic analysis, blood samples were obtained from a subgroup of patients at 10, 30 minutes and 1, 2, 4, 8, and 24 hours after initiation of pemetrexed infusion. Population-PK modelling was done to estimate the total exposure to pemetrexed, expressed as area under the curve (AUC) of pemetrexed per patient. The relation between AUC during cycle 1 (AUC1) and OS/PFS in treatment-naive patients was examined using Cox regression analyses. The difference in mean AUC1 between patients with and without grade ≥ 3 chemotherapy-related AEs, according to CTCAE 4.03 during the treatment duration of 4 cycles was compared in all patients.

The concentrations of pemetrexed were quantified in 106 of 165 patients and 24-hour PK was available for 15 patients. The median estimated AUC1 was 201 mg·h/L (interquartile range: 179-224). By univariate analysis, AUC1 did not predict for PFS/OS in 95 treatment-naive patients. By multivariable analysis adjusting for prognostic factors, including sex, disease stage, and WHO performance score AUC1 was also not predictive of PFS/OS (OS hazard ratio [HR] 1.05; 95% confidence interval [CI], 1.00-1.11; PFS HR 1.03; 95% CI, 0.98-1.08).

Compared to 51 patients without grade ≥ 3 chemotherapy-related AEs, 55 patients with grades ≥ 3 chemotherapy-related AEs had significantly higher AUC1 values of 220 versus 191, respectively ($p < 0.001$). Separating ≥ grade 3 chemotherapy-related AEs into clinical and laboratory AEs yielded identical results. Visser *et al.* Abstract 132PD

Practice point and future research opportunities

Currently, there are no clinically useful predictors of efficacy and toxicity to pemetrexed in advanced NSCLC. This study did not find total systemic exposure to pemetrexed to predict for PFS/OS. However, pemetrexed was significantly associated with more frequent occurrence of severe chemotherapy-related AEs. Although the impact of peak concentrations on efficacy remains unclear, these findings suggest that lower dosage might prevent severe toxicity while maintaining efficacy.

A propensity-matched analysis of the Surveillance, Epidemiology, and End Results (SEER) registry reveals radiotherapy improves survival in stage IV NSCLC

Rui Zhang, Cancer Centre, Renmin Hospital of Wuhan University, Wuhan, China and colleagues reviewed data of patients with stage IV non-small cell lung cancer (NSCLC) contained in the Surveillance, Epidemiology, and End Results (SEER) registry from January 2010 to December 2012. Propensity score (PS) analysis was done using a 1:1 nearest neighbour matching method to ensure that the characteristics were well-balanced across all comparison groups by histological types and metastatic sites. Overall survival (OS) and cancer-specific survival (CSS) were evaluated using Kaplan-Meier and Cox proportional hazardous models.

The investigators discovered a trend towards improved OS and CSS when radiotherapy was used to treat stage IV NSCLC patients for any metastatic sites and for any histological types except adenocarcinoma. Survival of NSCLC patients with metastasis to the brain was significantly improved with radiotherapy ($p < 0.001$), especially for adenocarcinoma ($p < 0.001$).

In stage IV lung cancer patients with squamous cell carcinoma, radiotherapy for any metastatic sites universally improved the OS ($p < 0.001$), and CSS ($p < 0.001$). Radiotherapy was associated with improved OS ($p < 0.001$) and CSS ($p = 0.012$) in stage IV patients poly-metastatic disease involving metastases in two or more sites. In patients with stage IV squamous cell carcinoma without metastasis, radiotherapy administered most likely to the primary site, significantly improved the survival ($p < 0.001$). Zhang *et al.* Abstract 131O

Practice point and future research opportunities

The survival advantage of radiotherapy in patients with stage IV NSCLC has not been adequately evaluated; these findings from a PS-matched patient cohort from the large SEER database support radiotherapy as improving survival of patients with metastatic NSCLC. Careful selection of patients as candidates for radiotherapy in metastatic NSCLC is necessary.

METASTASES TO AND FROM THE LUNG

High physician confidence does not predict the rate or types of treatment change for cases discussed at a thoracic multidisciplinary cancer conference

Christine Fahim, Health research Methods, Evidence and Impact, McMaster University, Hamilton, Canada presented findings from an analysis of the rate and type of decision change following evaluation of thoracic cancer patients in multidisciplinary cancer conferences (MCCs). The MCC comprised surgeons, oncologists, pathologists and radiologists and took place at a Canadian tertiary cancer centre. The treating physicians used a standardised MCC intake form to present cases describing a clinical question, the original treatment plan, and rated their confidence from 1 to 5 in the original plan. Major changes were defined as a change from upfront surgery to neoadjuvant treatment, definitive chemotherapy/radiation, or Stereotactic Body Radiation Treatment/Radiofrequency Ablation (SBRT/RFA) and as change from neoadjuvant or definitive chemotherapy/radiation or SBRT/RFA to surgery; or palliation/observation instead of definitive treatment. Minor changes included additional imaging, further staging investigations, repeat consultations, or changes in planned oncologic or surgical approach. The data were reported as frequencies, using Chi-square tests to compare groups at a $p < 0.05$ significance level.

The MCC reviewed 116 cases from June to December 2017. A re-review of imaging or pathology was needed in 111 cases (96%) with 70 (60%) cases resulting in a treatment change. Of these, 29 (41%) of changes were considered major and 41 (59%) of changes were deemed as minor. A commonly recommended major change (39%) was the use of neoadjuvant or definitive chemotherapy/radiation instead of upfront surgery, whereas minor changes primarily involved further staging investigations in 56% of cases.

High physician confidence in the original treatment plan did not significantly associate with the rate of change, which was 53% no change and 47% change, ($p = 0.073$), or with the type of change, which included 30% major and 70% minor ($p = 0.098$). Fahim *et al.* Abstract 200PD

Practice point and future research opportunities

This analysis revealed that 60% of cases discussed at a thoracic MCC resulted in a treatment change from the originally planned regimen, with 41% of these considered major changes, which were made despite high physician confidence in the original treatment plan, which did not significantly correlate with the rate or type of change. These data support the importance of continued implementation of MCCs.

MESOTHELIOMA

Analysis reveals that baseline endoglin levels potentially indicate improved PFS and/or OS with nintedanib in malignant pleural mesothelioma

Nick Pavlakis, Northern Cancer Institute, St Leonards, Australia presented findings from a biomarker analysis on behalf of colleagues from the randomised phase II/III LUME-Meso study of nintedanib plus pemetrexed/cisplatin versus placebo plus pemetrexed/cisplatin followed by nintedanib or placebo maintenance, in chemotherapy-naive malignant pleural mesothelioma (MPM) patients. Patients receiving nintedanib in addition to pemetrexed/cisplatin and as maintenance therapy in the phase II part of LUME-Meso demonstrated prolonged progression-free survival (PFS) compared to patients receiving placebo (hazard ratio [HR] 0.54; p = 0.010), as well as a trend toward longer overall survival (OS, HR 0.77; p = 0.319).

With observation that the greatest benefit occurred in patients with epithelioid tumours, plasma angiogenic factors and genomic markers were explored for potential associations with treatment outcome in the epithelioid population of the phase II part of the trial. This biomarker analysis evaluated the baseline plasma levels of 58 angiogenic factors by multiplex immunoassay (Human AngiogenesisMAP®, Myriad RBM). The investigators reviewed genes implicated in the nintedanib mechanism of action and/or the mesothelioma pathophysiology, including VEGFR1, VEGFR3, and mesothelin for known SNPs. The association of markers with the PFS and OS following nintedanib treatment was assessed by Cox regression and interaction tests with false-discovery rate (FDR) adjustment.

The epithelioid population consisted of 77 patients, of whom 71 patients had available angiogenic factor data and 67 had genomic data. Investigation of the angiogenic factors revealed that only endoglin showed a possible trend for association with improvement in both PFS and OS. The greater benefit with nintedanib was observed in patients with low baseline plasma levels of endoglin. An OS benefit was associated with major homozygous genotypes for two VEGFR3 single nucleotide polymorphisms (SNPs) rs307821 G/G and rs307826 A/A, which each showed a weak association with OS. A potential PFS benefit was associated with the VEGFR1 SNP rs9582036 A/A genotype.

The investigators noted that the FDR-adjusted interaction tests were not significant and had possibly been affected by the biomarker treatment associations, which were limited by small subgroup size, especially in the case of minor genotypes. Pavlakis *et al.* Abstract 213PD

Practice point and future research opportunities

Although the analysis was limited by small subgroup size, these findings represent the first biomarker results for nintedanib-treated patients with MPM, which showed potential signals for an improved PFS and OS benefit in patients with low baseline plasma endoglin levels and with major homozygous VEGFR1/3 genotypes. However, the study uncovered no clear association between the biomarkers evaluated and the improved PFS and OS that were demonstrated with nintedanib, making these results hypothesis-generating.

Multiplexed proteomics biomarkers for malignant pleural mesothelioma detection in blood

Ferdinando Cerciello, James Thoracic Centre, James Cancer Centre, The Ohio State University Medical Centre, Columbus, USA explained that blood biomarkers have not routinely been applied for the diagnosis of malignant pleural mesothelioma (MPM), prompting this investigation of a multiplexed biomarker signature composed of 6 glycopeptides. The signature was used to diagnose MPM in blood samples using mass spectrometry based targeted proteomics. The investigators applied the targeted proteomics technology selected reaction monitoring (SRM, also known as multiple reaction monitoring – MRM) to evaluate more than 400 serum samples obtained from patients with early and advanced staged MPM, as well as asbestos exposed donors contained in biobanks in the USA, Australia and Europe. The samples were enriched for N-linked glycoproteins using hydrazide chemistry. After tryptic digestion, N-linked glycopeptides were separated by liquid chromatography before analysis on a triple quadrupole mass spectrometer (LC-MS/MS). Logistic regression was fitted on a training set of 212 samples followed by evaluation of predictive accuracy of the signature in a validation set of 193 samples.

The proteomics platform for serum processing on 96-well plates and LC-MS/MS analysis had coefficient of variation between 2.0 and 11.4% for peptide quantification over more than 700 measurements, and standard deviation of 0.42 for processing more than 400 replicates. The predictive accuracy for MPM discrimination was significantly higher using multiplexed biomarkers by mass spectrometry compared to using single biomarkers alone.

The multiplexed proteomics signature was able to separate MPM patients from asbestos-exposed donors with an area under the receiver operating characteristic curve of 0.72 in the validation set; the AUC for discriminating early stage MPM from asbestos exposed donors was 0.74. Predictive accuracy of the proteomics signature was not inferior to the currently best available MPM blood biomarker soluble-mesothelin related peptides measured in the samples of the validation set using an enzyme-linked immunosorbent assay that has been approved by the US Food and Drug Administration. Furthermore, the signature was significantly associated with survival of MPM patients after treatment. Cerciello *et al.* Abstract 214PD

Practice point and future research opportunities

Mass spectrometry based proteomics biomarkers have potential for the diagnosis of MPM in blood samples.

Multimodality therapy improves survival in patients with malignant pleural mesothelioma

Mariam Hassan, Suez Canal University, Ismailia, Egypt presented findings on behalf of colleagues from an analysis of data from 681 patients with malignant pleural mesothelioma (MPM) contained in the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2013. Patients of all age groups, races, AJCC stages I-IV, and histopathological variants were included and stratified according to whether they received surgery alone, surgery followed

by radiotherapy, surgery and chemotherapy, or triple modality comprising surgery, chemotherapy, and radiotherapy.

A regimen of surgery and chemotherapy had been most often administered to patients, with fewer than 20% of patients receiving triple therapy. Of the 681 patients with MPM included in the analysis, 176 (25.8%) received only surgery, 74 (10.9%) had surgery followed by radiotherapy, 307 (45.1%) had surgery and chemotherapy, and 124 (18.2%) patients received a combination of surgery, chemotherapy, and radiotherapy. One-year survival rates of patients with MPM were highest in patients receiving multi-modal treatment, who demonstrated one-year survival rates of 79.6% compared to 70.3% in patients treated with surgery followed by radiotherapy, 62.2% in patients receiving both surgery and chemotherapy, and 37.9% in patients having only surgery ($p = 0.000$).

In the cohort of patients receiving multiple modality therapy, one-year survival was achieved by 3 (100%) patents with nodal stage N3, 22 (73.7%) patients with N2, 35 (87%) N1 patients, and 63 (77.7%) patients with N0 involvement ($p = 0.02$). Age was also a significant factor with more patients aged fewer than 80 years surviving for one year than patients over the age of 80 ($p = 0.000$). Patients with epithelioid or biphasic histopathology fared better with 81.9% and 89.1% of these patients achieving one-year survival compared to just 15.0% of patients with sarcomatoid tumours ($p = 0.000$). One-year survival rates according to AJCC stage were 82.4%, 85.5%, and 71.0% for patients receiving multimodality treatment and stage II, III, and IV, respectively. Hassan *et al.* Abstract 215PD

Practice point and future research opportunities

Malignant pleural mesothelioma is no longer considered a rare disease and has an escalating incidence, making it necessary to develop innovative treatment modalities. Findings from this study show survival rates of MPM patients are the highest when receiving combination of surgery, chemotherapy and radiotherapy. Age, nodal status and having epithelioid or biphasic histology associated with improved survival, but more study is needed in prospective trials.

When to perform radical surgery in patients with non-epithelioid malignant pleural mesothelioma

Loic Lang-Lazdunsk, Lung Centre, Cromwell Hospital, London, UK presented findings in support of multimodality therapy, including radical surgery, in patients with epithelioid and non-epithelioid malignant pleural mesothelioma (MPM). Professor Land-Lazdunsk and colleagues conducted this analysis of a prospective database of patients operated on for MPM since September 2004. Treatments delivered to the patients included extended pleurectomy/decortication, hyperthermic povidone-iodine pleural lavage, prophylactic radiotherapy, and systemic platinum-based chemotherapy. Hyperthermic povidone-iodine pleural lavage and extended pleurectomy/decortication were done in all 139 patients, and all patients received prophylactic radiotherapy at 21 Gy. All but 9 patients received 4 to 6 cycles of chemotherapy; 5 patients did not receive adjuvant chemotherapy and 4 received fewer than 4 cycles. Systemic chemotherapy was delivered to 17% of patients prior to surgery. The median age was 64 years and 80% of

patients were male. Follow-up monitoring was done using PET–CT until death. Survival and prognostic factors were evaluated by the Kaplan–Meier method, log–rank test and Cox regression analysis.

No 90–day mortality occurred in patients treated with multimodality therapy, which consisted of surgery, chemotherapy, and radiotherapy. Postoperative complications occurred in 39.6% of patients and 9 patients had reoperation within 30 days. Second–line therapies were given to 52% of patients. Two patients received cyber knife therapy and 3 patients had late reoperations for focal relapse.

Stage I tumours were identified in 7.2% of patients, stage II in 24.4%, stage III in 54%, and stage IV in 14.4% of patients. Tumour histopathology showed 96 patients had epithelioid and 43 patients had non–epithelioid type tumours.

Multimodality therapy especially benefited patients with epithelioid histology. After a median follow–up of 50 months, the median overall survival was 35 months (95% confidence interval [CI], 26.3-43.7) in patients with epithelioid histology compared to 18 months (95% CI, 15.1 - 20.9) for patients with non-epithelioid histology (p = 0.000037). By the end of follow-up, 92 patients had died. On multivariate analysis, macroscopic complete resection and epithelioid histology emerged as independent prognostic factors of long–term survival on multivariate analysis. Lang-Lazdunsk *et al.* Abstract 135PD

Practice point and future research opportunities

Multimodality therapy including extended pleurectomy/decortication and hyperthermic povidone-iodine pleural lavage is safe and well-tolerated; most patients can receive further therapies at the time of disease progression. While MPM carries a poor prognosis, patients with epithelioid histology achieve prolonged survival and complete surgical resection also improved survival. Patients with non-epithelioid histology have a modest survival benefit and radical surgery should be offered only to those with early-stage disease.

THYMIC CARCINOMA

Nivolumab benefit unresolved in unresectable or recurrent thymic carcinoma

Takashi Seto, Department of Thoracic Oncology, National Kyushu Cancer Centre, Fukuoka, Japan discussed the results from the open-label, two-stage, multicentre, single-arm, phase II PRIMER study of nivolumab in 15 patients with unresectable or recurrent thymic cancer. Of these patients, all were Japanese and 12 were male with a median age of 55 (range, 34 to 70) years. Squamous histology was confirmed in 13 patients. Most (11) patients were ECOG performance status 1, and all had measurable disease that had progressed after at least one previous platinum-based chemotherapy or radiotherapy treatment. Half of the patients were ex-smokers and one was current. None of the patients had a history of autoimmune disease. Nivolumab was administered at 3 mg/kg i.v. every 2 weeks for a median of 8 cycles (range, 3 to 29).

PRIMER had a planned sample size of 15 patients for the first stage and was to proceed to a second stage of enrolling an additional 18 patients with the observation of one or more responses with a threshold response rate of 5%. At the primary analysis, which was carried out after a median follow-up of 3.8 months (range, 1.4 to 12.0) weeks, the response rate by central review was 0% (95% confidence interval [CI], 0–21.8) and the study was not taken forward.

However, Dr. Seto noted that 11 of the patients had achieved stable disease with nivolumab, which lasted for 24 or more weeks in 5 of these patients, providing a disease control rate (DCR) of 73.3% (95% CI, 44.9-92.2). Two patients remain on nivolumab. After nivolumab, the median progression-free survival (PFS) was 3.8 months (95% CI, 1.9-5.6) and the 12-month PFS rate was 13.3% (95% CI, 2.2-34.6). Median overall survival (OS) was NA (95% CI, 11.3-NA) and 12-month OS was 60.0% (95% CI, 31.8-79.7).

No patients discontinued the study due to an adverse event (AE). One patient experienced a treatment-related serious AE of grade 3 increased AST.

The authors summarised that no tumour shrinkage was observed with nivolumab suggesting that further development of nivolumab is not recommended in previously treated unresectable or recurrent thymic carcinoma, even though the study had a very small number of patients. UMIN000022007. Seto *et al.* Abstract 112O

Practice point and future research opportunities

Thymic carcinoma carries a poor prognosis with limited treatment options, especially after relapse. Current treatment primarily consists of chemotherapy with cisplatin, doxorubicin, and cyclophosphamide (CAP). Data from RYTHMIC, a French thymic carcinoma network showed that CAP provided 36% partial response (PR), 36% stable disease (SD), and 28% disease progression.

The EORTC is organising the NIVOTHYM study, which is currently accruing patients with relapsed and/or advanced thymoma B3 and thymic carcinoma who are not candidates for curative-intent radical treatment and have undergone at least one previous line of platinum-based chemotherapy for advanced disease. The rationale for investigating immunotherapy in these patients includes: These tumours frequently show high PD-L1 expression, and findings from a phase II trial of thymic carcinoma patients treated with pembrolizumab showed an objective response rate of 23% including 3% complete response, 22% PR, and duration of response of 22 months; the median PFS was 4.2 months.

Regarding the PRIMER study, 12 weeks may have been too short time to evaluate a primary endpoint; nevertheless, SD and a 12-month OS rate of 60.0% were demonstrated.

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Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

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