2016 ELCC European Lung Cancer Conference

13-16 April 2016

Geneva, Switzerland

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Summary

The sixth European Lung Cancer Conference (ELCC) was held in Geneva, Switzerland, from 13 to 16 April 2016. The Conference was organised by the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC), with partner societies European Society for Radiotherapy & Oncology (ESTRO), European Society of Thoracic Surgeons (ESTS) and European Thoracic Oncology Platform (ETOP), bringing together some of the most important organisations representing thoracic oncology specialists to provide cutting-edge science and education. The broad scientific programme featured in-depth discussion and analysis of the latest findings and practice changing advances in thoracic cancers treatment.

The scope of this report is to present the scientific highlights of the ELCC 2016 Conference.

Introduction

This years' Conference attracted 2,247 medical and healthcare professionals from Europe and around the world who assembled at this unique event to share knowledge on the latest advances in lung cancer. This attendance figure represents a 34.1% increase over ELCC 2015 and gives testimony to the ever-increasing importance of this meeting in the field of oncology. Attendees consisted mostly of 1,823 delegates, although 281 exhibitors and industry representatives, 103 faculty members and 40 members of the press were also in attendance. The highest proportion, 10.7% of delegates, represented the host country, Switzerland. But the conference was not just a local event; delegates came from approximately 80 different countries world-wide, with 8.7% off delegates travelling from China, 8.2% from the United States, and 7.3% from the United Kingdom. The next highest proportion of delegates came from Germany, Austria, Italy, Belgium, Spain, and France in that order.

The participants in ELCC 2016 comprised about a quarter (24.5%) medical oncologists, 12.1% medical staff, 9.4% radiation oncologists, 9.4% chest physicians, 4.4% basic researchers, as well as medical professionals, including geneticists, pathologists and oncology nurses, among others. While participants showed a broad range of interest covering the spectrum of the field of cancer, the majority of those attending (79%) shared chest malignancies as their field of interest.

Of the 260 abstracts that were submitted, 215 were accepted. The abstracts chosen for presentation and discussion reflected the foremost research and most current treatment strategies in thoracic oncology that will influence patient care. Of these, 16 were chosen for oral presentation, 22 for poster discussion, and 177 were presented as posters, thus providing an accessible, well-rounded programme. The majority (79%) of abstracts focused on advanced non-small cell lung cancer (NSCLC), with 35% dealing with the field of tumour biology and pathology, and 29% tackling translational research. An equal 24% of abstracts each addressed prevention, early detection epidemiology, tobacco control, and miscellaneous topics. Early stage lung cancer (20%), metastases to and from the lung (16%), locally advanced NSCLC (12%), mesothelioma (8%), imaging and staging (7%), and small-cell lung cancer (SCLC) (6%) accounted for the remainder of the abstracts. The oral presentations and poster discussion sessions featured faculty that placed abstract findings into clinical context and discussed how the results may impact the current standard of care. In addition, questions from a well-informed audience provided lively discussion in all sessions.

This year's Conference included combinations of immunotherapy and chemotherapy currently being tested, and evaluation of the utility of plasma-based assays for mutation monitoring in disease progression. Investigators discussed updates from the SQUIRE trial in patients with stage IV squamous NSCLC and EGFR expressing tumours, plus presentations on the third generation tyrosine kinase inhibitor (TKI) targeting the T790M mutation, osimertinib, both in pre-treated patients on progression, and also as first-line therapy.

A brief summary of some of the diverse scientific findings presented at ELCC 2016 follows.

TUMOUR BIOLOGY AND PATHOLOGY

Comprehensive molecular profiling shows disparity between primary NSCLC tumours and metastases

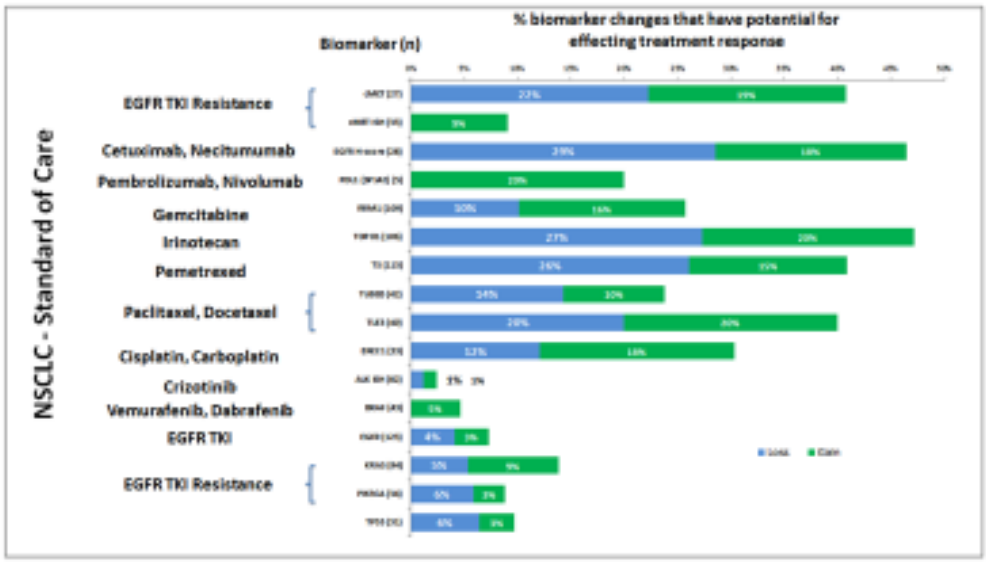
Zoran Gatalica of Caris Life Sciences, Phoenix, USA, reported that differences of up to 47% in the expression rates of biomarkers between the primary non-small cell lung cancer (NSCLC) tumour and metastatic sites were detected using comprehensive molecular profiling. The investigators used 10,764 profiled NSCLC samples from a Caris Life Sciences tumour bank and categorised them as primary tumours, lymph node (LN) metastases, and distant organ metastases to determine sequences that were biomarkers of site-specific actionable targets. The biomarkers were detected using immunohistochemistry (IHC), in-situ-hybridization (ISH) and by Sanger and next generation sequencing (NGS) methods. Biomarkers with sequences that could be targeted by current therapeutic agents were compared between primary, LN metastases, and distant metastatic tumours in this sample cohort and confirmation was done in a cohort of 20 patients with matched samples.

Numerous biomarkers were detected in both squamous cell cancer and adenocarcinoma that could be acted upon by current targeted biological therapies: These samples had a 2.4% ALK expression rate, 1.0% had ROS1 rearrangement, 2.9% of samples contained HER2, and 4.0% had cMET amplification. EGFR overexpression was detected in 49.2% of these samples, 29.5% showed gene amplification, and 12.3% of samples showed mutations.

Biomarkers targetable by inhibitors of immune checkpoint inhibitors were detected, including 25% PD-L1 expression, as well as sequences targeted by chemotherapeutic agents, such as BRCA1 and 2, ERCC1, TUBB3, RRM1, TOPO1, and thymidylate synthase (TS).

Several biomarkers showed significantly different rates of expression, amplification/fusion, and mutation between matched primary versus lymph node or distant metastasis samples. Alterations that occurred at higher frequency in the LN metastases of lung adenocarcinomas than in the primary tumours included: ALK positivity by IHC (8% versus 1%), PD-L1 rates (36% versus 25%), and ROS-1 re-arrangement rates (3% versus 1%). EGFR detection in LN metastases versus primary tumour was 50% versus 42% by IHC and 39% versus 28% by ISH, respectively. Distant organ metastases displayed higher cMET amplification of 7% compared with 3% in primary tumours.

Biomarkers that display significantly different rates of expression, amplification/fusion and mutation in matched primary vs. metastases (lymph node or distant metastasis) in NSCLC (n=154; 130 ADC, 14 SCC)



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In squamous cell carcinomas, higher ALK expression at a rate of 10% was seen in LN metastases than in the primary site where the ALK expression rate was 1%. The PD-L1 expression rate in squamous cell carcinomas was also higher at 42% in LN metastases compared with 33% in the primary tumour.

Trends of expression rates that were observed in the unmatched cohort were confirmed in the cohort of patient-matched tissue samples, where gains in PD-L1 expression, cMET amplification, and TP53 mutations and losses in KRAS mutations were observed in both cohorts of samples. Gatalica *et al.* Abstract PD1.

Practice point and future research opportunities

These findings highlight the importance of the extent and timing of tissue sampling for molecular profiling. Comprehensive genomic profiling can be used successfully to identify actionable targets in tumours, but spatial and temporal differences (heterogeneity) in the expression of predictive biomarkers between primary NSCLC tumours and metastases to the lymph node or distant organs may be substantial. The availability of recently developed targeted therapies and the predictive value of their biomarkers, together with the heterogeneity displayed between primary tumours and metastases mandate thoughtful profiling of tumour samples in order to achieve maximum therapeutic response.

Co-amplification of PD-L1/PD-L2 genes associates with PD-L1 protein expression, KRAS mutation, and histology in NSCLC patients

Sergi Clavé, Pathology Department, Hospital del Mar in Barcelona, Spain and colleagues conducted a study to determine whether PD-L1 copy number alterations (CNAs) determine the prevalence of PD-L1 and the ligand expression in non-small cell lung cancer (NSCLC) tumour cells. PD-L1 amplifications have been reported in approximately 5% of NSCLC and co-amplification of PD-L1 and PD-L2 genes on chromosome 9p24.1 has been suggested as a predictor of response to anti PD-1/PD-L1 immune blockade. The team assayed DNA from 67 adenocarcinoma and 8 squamous cell carcinoma patients for PD-L1 and PD-L2 on chromosome 9p24.1 CNAs using fluorescence in situ hybridization (FISH) and for PD-L1 protein expression by immunohistochemistry (IHC) and evaluated the patients' clinical data, plus EGFR and KRAS mutational status and ALK rearrangements.

Of these NSCLC patients, 33 (44%) had PD-L1/PD-L2 CNAs comprising 5 (6.7%) gene co-amplifications, 6 (8%) high polysomy, and 22 (29.3%) cases of chromosome 9 trisomy. High PD-L1 expression was found in all amplifications, whereas increased protein expression was seen in just 2 cases of high-polysomy. No PD-L1 expression was found in samples wherein no PD-L1/PD-L2 CNAs were detected. All of the 5 co-amplifications were found in male patients who were current or former smokers having a median age of 62 (range: 53 to 72) years. Among these patients, 3 had tumours displaying acinar/solid adenocarcinoma histology. Of note were 2 patients with squamous cell carcinoma histology ($p = 0.035$) and 3 patients also harbouring KRAS mutations ($p = 0.021$).

Since the PD-L1/PD-L2 amplifications correlated with the expression of the PD-L1 receptor, the authors recommend that the analysis of PD-L1 FISH CNAs be further investigated and their predictive and prognostic roles be fully elucidated, including the associations with histology and KRAS mutations. Clavé *et al.* Abstract 4P.

Practice point and future research opportunities

This analysis of PD-L1 copy number alterations demonstrated an association between gene co-amplifications and higher PD-L1 protein expression and that samples negative for PD-L1/PD-L2 copy number alterations corresponded with no PD-L1 protein expression. The presence of PD-L1 copy number alterations also associated with small-cell carcinoma histology and KRAS mutation. These results warrant further investigation to establish PD-LI copy number alterations as prognostic and predictive of response to immune blockade therapies.

PREVENTION, EARLY DETECTION, EPIDEMIOLOGY, TOBACCO CONTROL

Novel circulating microRNA signature assay may be a potential non-invasive test for early detection of NSCLC

Thomasz Powrózek, Pneumonology, Oncology and Allergology, Medical University of Lublin, Lublin, Poland, and colleagues investigated the difference in microRNA (miRNA) expression in cancer patients compared with healthy individuals. They evaluated whether a panel of six novel circulating miRNAs-448, 506, 944, 3662, 4316, and 4478 could serve as biomarkers of early stage non-small cell lung cancer (NSCLC). The expression of this panel was detected using qRT-PCR method in plasma samples obtained from 45 patients with stage I-IIIA and 35 patients with stage IIIB-IV NSCLC that were compared with expression in 80 healthy individuals. The diagnostic accuracy of the panel was assessed using logistic regression model and receiver operating curves (ROC) with area under curve (AUC) analysis.

Four miRNA in the panel, miRNA-448, 944, 3662, and 4478 were expressed at significantly higher levels in the plasma of lung cancer patients compared with healthy individuals ($p < 0.0001$). This signature had high diagnostic power for detection of operable stages I through IIIA of NSCLC, showing sensitivity of 84.8% and specificity of 96.6% (AUC=0.930). Expression of miRNA-944 showed diagnostic accuracy for detection of operable squamous cell carcinoma, with sensitivity of 85.7% and specificity of 90.3% (AUC=0.982). Expression of miRNA-3662 was highly diagnostic for operable adenocarcinoma, with sensitivity of 82.4% and specificity of 93.5% (AUC=0.926). No diagnostic value in patients with NSCLC was observed for expression of miRNAs-506 and 4316.

The authors concluded that these findings confirm that the gene encoding miRNA-944 is localised within an intron of the p63 gene since this expression is a marker of squamous differentiation. Also, the miRNA-3662 sequence is complementary to mRNA of suppressor genes (PTAR1, SEPT10 and NPR3), which are disordered in adenocarcinoma differentiation. Powrózek *et al.* Abstract 30PD

Practice point and future research opportunities

Since miRNA can be detected in blood samples this may serve as a non-invasive liquid biopsy for NSCLC, either used alone or in combination with computed tomography lung screening. This novel signature of four circulating miRNAs associated with early stage NSCLC and showed good sensitivity and specificity. Two individual miRNAs showed good sensitivity and specificity as biomarkers: miRNA-944 associated with early differentiation of squamous cell carcinoma, and miRNA-3662 was highly expressed in early adenocarcinoma. Further study of this panel and confirmation of these results are warranted.

DNA methylation of SHOX2 and PTGER4 as a plasma-based tool to differentiate between patients with malignant and benign lung disease

Lead author Gunter Weiss, Epigenomics AG, Berlin, Germany noted that the DNA methylation panel of the genes SHOX2 and PTGER4 has recently been successfully evaluated in three independent case-control studies comprising a total of 330 plasma specimens from patients with lung cancer as compared with healthy individuals, demonstrating area under the curve (AUC) of 91% to 95%. In the case-control study presented at ELCC, this same panel was assessed as a marker panel in patients with malignant or benign lung disease (BLD) using 172 plasma specimens obtained from 50 patients with lung cancer, 50 BLD patients and 72 healthy individuals.

The investigators developed a triplex real-time PCR assay for methylated DNA of SHOX2 and PTGER4 with ACTB as a control assay. Total DNA was extracted from 3.5 ml plasma samples, purified, and assayed by PCR in triplicate. Receiver operating characteristic and the AUC were analysed for the marker panel, which showed significant discriminatory power in distinguishing lung cancer cases from the remaining subjects (AUC = 0.88), including BLD patients (AUC = 0.85), and healthy subjects (AUC = 0.89).

With specificity fixed at 95% the sensitivity of the panel to detect lung cancer was 60%, and at fixed sensitivity of 94%, specificity was 56%. The methylation markers yielded similar profiles in both BLD subjects and healthy individuals (AUC = 0.55). However, the clinically important comparison between 18 patients with chronic obstructive pulmonary disease (COPD) and the LC group showed a significantly different profile (AUC = 0.79). The authors plan to further develop this marker panel as a non-invasive diagnostic tool that may provide clinical utility in differentiating between patients with lung cancer from patients with other lung disease and from healthy individuals. Weiss *et al.* Abstract 31PD.

Practice point and future research opportunities

Current guidelines in the USA recommend screening for lung cancer by low-dose computed tomography (LDCT) in high-risk patients. However, European guidelines do not recommend LDCT screening due to the controversy surrounding the definition of high-risk groups and the possible impact of LDCT false positive findings. This study suggests that DNA methylation markers, SHOX2 and PTGER4, could be used to distinguish lung cancer patients from patients with non-malignant diseases with high sensitivity and a reasonable false positive rate. This marker panel shows promise for use combination with current imaging techniques to improve lung cancer risk stratification.

TRANSLATIONAL RESEARCH

PD-L1 blockade with durvalumab plus gefitinitib shows promise in EGFR mutated NSCLC

Donald Gibbons, The University of Texas MD Anderson Cancer Center, Houston, USA reported first results from an expansion phase of a phase I open-label multicentre study evaluating the safety and tolerability of combined therapy of durvalumab (MEDI4736) plus gefitinib in tyrosine kinase inhibitor (TKI)-naive patients with non-small cell lung cancer (NSCLC) and sensitising EGFR mutations; exon 19 deletion was detected in 11 patients and 8 patients had exon 21 L858R mutation.

Durvalumab is a human IgG1 monoclonal antibody that selectively blocks interaction of programmed death ligand-1 (PD-L1) with PD-1 and CD-80. Treatment arms of the ongoing expansion study have 10 patients each: patients in arm 1 receive concurrent durvalumab at 10 mg/kg every 2 weeks plus gefitinib at 250 mg once-daily and arm 2 patients received 4 weeks of priming gefitinib monotherapy followed by concurrent durvalumab plus gefitinib at the same dose as arm 1. Patient characteristics are balanced across both arms. The trial's primary endpoints are safety and tolerability and the secondary endpoints include tumour response by RECIST 1.1, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity.

Efficacy was assessed at ≥8 weeks for 19 patients; 9 patients in arm 1 and 10 patients in arm 2 had evaluable data. At data cut-off on 15 September 2015, follow-up was ≥3 months for all patients. The investigator-determined best objective response rate (ORR) in arm 1 was 78% and 80.0% in arm 2. One (11.1%) patient in arm 1 achieved complete response. Partial response was achieved in 6 (67%) and 8 (80.0%) patients in arms 1 and 2, respectively. Stable disease lasting 8 weeks or longer was observed in 2 (22.2%) in arm 1, and one (10.0%) patient in arm 2. Stable disease lasting 24 weeks or longer was observed in 1 patient (10%) in arm 2.

The gefitinib/durvalumab combination was tolerable in most patients. The most frequently reported treatment-related adverse events (AEs) of any grade occurring in 4 or more patients included diarrhoea, reported by 80% and 60% of patients in arms 1 and 2, respectively. In arm 1, 70% of patients reported increased ALT, 60% of patients had rash, 40% of patients reported either increased AST, pruritus or nausea, and 30% of patients experienced dry skin. In arm 2, 60% of patients reported increased ALT or pruritis, 50% of patients reported either increased AST or dry skin, 40% had rash and 10% of patients reported nausea. Trial discontinuation due to treatment-related CTC grade 3/4 AEs was reported only in arm 2, wherein 3 patients stopped treatment due to increased ALT and/or AST and one patient discontinued due to pneumonitis. No significant PK or PD interactions were observed nor were any anti-drug antibodies detected. The 10 mg/kg durvalumab plus 250 mg gefitinib regimen is being brought forward for continued evaluation in the ongoing trial. NCT02088112. *et al.* Abstract 57O.

Practice point and future research opportunities

These early results from a trial of durvalumab plus gefitinib demonstrated tolerability and encouraging anti-tumour activity in TKI-naive patients with NSCLC and EGFR

mutations. Which patients will benefit from combination therapies of checkpoint inhibitors and whether concurrent or sequential administration is optimal are being investigated. PD-L1 immunohistochemistry may predict the likelihood of response to anti-PD-1/PD-L1 therapy. However, anti-PD-1/PD-L1 strategies are established as second-line NSCLC treatment, showing response rates of up to about 20%. Responses with anti PD-1/PDL-1 agents are durable, and have resulted in remarkable long-term survival. Toxicity with these agents is less, in general, than that experienced with chemotherapy: Toxicity is seen in 50 to 69% of patients, grade 3/4 treatment-related adverse events occur in 8% to 16% of cases, specific immune-related grade 3/4 adverse events, and adverse events leading to treatment discontinuation are each seen in approximately 5% of patients.

The combination of a checkpoint inhibitor and a TKI is being investigated in several combinations in various trials. EGFR-TKIs represent a strong standard therapy and PD-L1 expression seems to be upregulated in early-stage EGFR mutation positive NSCLC, providing a clear rationale. However, clinical data in advanced disease show lower response rates to anti-PD-1/PD-L1 therapies in EGFR mutated tumours. Furthermore, overlapping toxicities may occur.

Immunotherapy combinations with TKIs have not demonstrated an overall response rate that is obviously better than with TKIs alone; responses may be more durable, but it is too early to tell. Sequential administration or pemetrexed combinations may improve response rates. Immunotherapy combined with TKIs show a sum of two different toxicity patterns with no “dangerous liaisons”.

Patient age and metastases alter EGFR mutation detection in plasma

Nicola Normanno, Istituto Nazionale Tumori, Fondazione Pascale, Napoli, Italy and colleagues used data from patients participating in the large non-interventional ASSESS trial to evaluate whether the detection of EGFR mutations in circulating free tumour-derived DNA in plasma may be altered by factors such as clinical characteristics or patient demographics. The investigators compared the accuracy of EGFR mutation-positive detection in plasma with detection in the tumour in terms of sensitivity, specificity, and concordance using the Coughlin method for covariates that included gender, age, ethnicity, smoking status, disease stage, WHO performance status (PS), time since diagnosis, metastases, and the number of organs with metastases.

Matched tumour and plasma samples were available from 1162 patients enrolled in ASSESS; of these, 189 patients had EGFR mutation-positive tumours, 126 patients were aged 65 years and older and 63 patients were younger than 65 years. Detection of EGFR mutation in plasma was higher in younger patients with mutation-positive tumours; 63.5% of patients aged less than 65 years had detectable EGFR mutation in plasma (95% CI 50%, 75%) compared with 37.3% of patients aged ≥65 (95 % CI 29; 46; interaction p = 0.0002)

EGFR mutation-positive detection in plasma increased as the number of organs with metastases increased; sensitivity with metastasis to one organ was 35.9% (95% CI 27, 46) versus 60.5% (95% CI 43, 76) with 2 involved organs, and sensitivity increased to 69.4% (95% CI 52, 84) with 3 or more involved organs. Similarly,

increased sensitivity was associated with higher metastatic grade, where sensitivity was 63.4% (95% CI 52, 74 in M1b versus 22.8% (95% CI 13, 36) in metastatic grade M1a (interaction p = NS).

Detection of EGFR mutation in plasma was unaffected by other variables such as gender, ethnicity, smoking status, and PS. The time since diagnosis ≤ 0.66 versus > 0.66 months also did not alter the ability to detect EGFR mutation in plasma (p = 0.7023). NCT01785888. Normanno *et al.* Abstract 58O.

Practice point and future research opportunities

The ability to detect EGFR mutation in circulating free tumour-derived DNA in plasma is compromised by increased patient age and is improved in patients with a higher metastatic tumour burden. Accurate description of the mutational status of EGFR and other key targets is essential over the course of the disease. Mutation detection from circulating free tumour-derived DNA in plasma is less accurate than biopsy but is a minimally invasive alternative. Further studies are needed to confirm these findings and to elucidate the underlying biological mechanisms.

EGFR mutation subtypes associate with specific clinical and demographic characteristics of patients with advanced NSCLC: Pooled analysis of IGNITE and ASSESS data

Baohui Han, Department of Respiratory Medicine, Shanghai Chest Hospital, Jiao Tong University, Shanghai, China and colleagues reviewed pooled data of 1242 patients with advanced non-small cell lung cancer (NSCLC) and EGFR mutations participating in the IGNITE and ASSESS trials to determine whether the frequency of EGFR mutation subtypes varies across clinical and demographic groups. The investigators evaluated the association between the presence and subtype of mutation with ethnicity, age (with 65 years as cutoff) smoking status, gender, adenocarcinoma/non-adenocarcinoma histology, current disease stage, WHO performance score, and the number of organs with metastases by multinomial logistic regression model using stepwise forward selection. Exon 19 deletions were used as reference.

This analysis revealed an association between disease stage III versus IV and the presence of an EGFR mutation (odds ratio [OR]) 0.56; 95% CI 0.40, 0.81], and stage IIIB versus IV (OR 0.62; 95% CI 0.47, 0.81).

Rare mutational subtypes as compared with L858R/Exon 19 deletions were seen more often in smokers than never-smokers, OR 2.6; 95% CI 1.5, 4.5 (p = 0.0005). Heterogeneity in the EGFR subtype of mutation was observed for smoking status, age, ethnicity, and histology (p < 0.05). Caucasians, patients aged less than 65 years, and patients with adenocarcinoma more often harboured exon 19 deletions than other mutational subtypes. Exon 20 insertions were only observed in patients with adenocarcinoma. The authors noted that the finding that patients with later stage disease were more likely to have EGFR mutation suggests selection favouring EGFR mutation positive cells occurs as the disease progresses. IGNITE (NCT01788163) and ASSESS (NCT01785888). Han *et al.* Abstract 59PD.

Practice point and future research opportunities

EGFR mutational subtypes were seen to associate with certain patient characteristics, such as smoking, where smokers were more likely to display more rare mutational subtypes than non-smokers. In addition, only patients with adenocarcinoma displayed exon 20 insertions. The finding that increased frequency of specific EGFR mutations patients with NSCLC associated with disease stage suggests selection that favours tumours with mutations takes place in disease progression.

Secondary drug resistance mutations monitored by circulating tumour DNA assay in patients with advanced ALK positive NSCLC

Paola Bordi, Medical Oncology Unit, Azienda Ospedaliera di Parma, Parma, Italy, underscored the urgent need for less invasive methods than rebiopsy to monitor the development of resistance mutations in patients with ALK-positive non-small cell lung cancer (NSCLC). These mutations accompany disease progression, which generally occurs at a median 9 to 10 months of crizotinib therapy. Her team monitored circulating cell-free DNA (cfDNA) for the identification of mechanisms of resistance on treatment with a second generation tyrosine kinase inhibitor (TKI) in 16 patients with ALK positive NSCLC who progressed on ALK-TKI treatment. Blood was obtained upon progression and DNA was extracted from plasma using QIAamp circulating nucleic acid kit (Qiagen®) and was tested for ALK secondary mutations and KRAS exon 12 mutations using the Digital Droplet PCR (ddPCR - BioRad®). All patients had stage IV adenocarcinoma. Of the 11 female and 5 male patients, 9 were never-smokers and 7 former-smokers. Median age was 53 (range: 40 to 81) years. Crizotinib had been given to 15 patients and 1 patient received ceritinib. ALK-TKIs were administered as first-line to 2 patients, second-line to 13, and as third line to one patient.

Second-generation ALK-TKIs demonstrated an enhanced spectrum of activity in crizotinib-resistant patients. Partial response was seen in 12 patients, 3 achieved stable disease, and one patient progressed. Median progression-free survival was 8 months. The brain was a site of progression in 12 patients; re-biopsy was plausible for just 5 tumours.

Analysis of cfDNA identified several mechanisms of resistance, including ALK gene mutations and amplification, as well as activation of bypassing signaling pathways, such as EGFR, KRAS or c-KIT. ALK secondary mutations were identified in 4 patients. One patient showed both p.L1196M and p.G1269A mutations; these levels decreased after 2 months of therapy with second generation ALK-TKI and these patients also showed tumour response. One patient had p.L1196M and one patients showed p.G1269A mutation. The 4th patient showed p.F1174L after initiation of second generation ALK-TKI. Upon developing resistance to TKI, 9 patients showed KRAS mutations p.G12D or p.G12V in their cfDNA; of these, 3 patients demonstrated both ALK and KRAS mutations. The authors suggest that KRAS mutations may play a role in developing resistance to ALK-TKIs. Bordi *et al.* Abstract 2PD.

Practice point and future research opportunities

Disease progression often occurs after a median of 9 to 10 months of crizotinib treatment. Mechanisms of resistance in ALK positive NSCLC patients treated with crizotinib have been identified, including ALK gene mutations and amplification and activation of bypassing signaling pathways like EGFR, KRAS or c-KIT. Re-biopsy is critical to monitor the development of resistance mutations but is often not possible to carry out, due to tumour location or patient preference. Assays of circulating cell-free DNA (cfDNA) represent a step forward towards non-invasive identification of mechanisms of resistance; resistance mutations can be detected by ddPCR in cfDNA in the plasma of patients with ALK-positive NSCLC, thereby providing an effective alternative to re-biopsy for response monitoring during treatment.

SMALL- CELL LUNG CANCER

Validation of the 7th and upcoming 8th TNM staging system in SCLC

The 7th and upcoming 8th TNM staging systems provide prognostic information that is additional to that provided by the 6th TNM version and the older limited disease (LD) versus extended disease (ED) VALSG system, according to Salomen Tendler, Oncology-Pathology, Karolinska University Hospital-Solna, Stockholm, Sweden. Professor Tendler and colleagues retrospectively reviewed the medical records of patients with small-cell lung cancer (SCLC) proven by histology/cytology that was diagnosed between January 2008 and January 2013 to evaluate the staging system in a Swedish cohort. All patients were required to have had computed tomography of the thorax/upper abdomen at baseline and patients with stage IA-IIB combined-type histology were excluded. The investigators revised patient files and reclassified SCLC diagnoses made by the VALSG system according to the 6th, 7th, and 8th TNM system, respectively, for clinical outcome in comparison to the VALSG system. Overall survival (OS) according LD/ED was reevaluated by the 6th, -7th, -8th editions of TNM; 4 separate multivariate models (adjusted for basic patient characteristics i.e. age, gender, WHO performance status and baseline levels of Hb, CRP and Na) were used.

The analysis included data from 249 patients with a median age of 69 years and 55% were female. Median OS was 6.2 months. Re-staging patients according to the 6th and 7th staging systems allowed a finer distinction of disease stage; 36 (14%) patients with LD and 213 (86%) patients were categorised into stages IIIA (12 [5%]; 14 [5%), IIIB 34 ([14%] 37[15%]), and IV 203([81%]; 198[80%]) by the 6th and 7th stage system, respectively. Upon multivariate analyses hazard ratios (HR) were also fine tuned by the subsequent grading systems. For stages IIIA, IIIB, and IV disease the HR was 0.59, 1.14, and 1.0 versus 0.55, 1.09, and 1 by the 6th TNM versus 7th TNM. The 8th version afforded an finer categorisation and increased predictive values;10 (4%) patients were stage IIIA (HR 0.40), 28(11%) IIIB (HR 1.06) , 28(11%) IIIC, (HR 1.32) 13 (5%) IVA (HR 0.99), and 176(71%) patients were stage IVB (HR 1.0). P values for VALSG and the 6th, 7th, and 8th staging systems were p = 0.0012, p = 0.02, p = 0.06, and p = 0.0004, respectively. Tendler *et al.* Abstract 91P.

Practice point and future research opportunities

These findings indicated that the 8th TNM classification system was the most accurate predictor of prognosis in patients with locally-advanced/metastatic SCLC.

Manchester prognostic scores associate with overall survival in SCLC

Sacha I. Rothschild, and colleagues from the Universitätsspital Basel in Basel, Switzerland reviewed data from 92 consecutive patients with small-cell lung cancer (SCLC) treated at their institution from January 2000 to December 2010 to assess the prognostic value of clinical factors and also to compare seven published prognostic scores for SCLC regarding overall survival (OS).

The results of univariate and multiple cox regression analyses of survival were presented at ELCC; the clinical data of the study population was previously

published (Hagmann R. J Cancer 2015). Of the 29 parametres assessed by univariate analysis, OS significantly associated with disease staging ($p < 0.001$), the number of metastatic sites ($p < 0.001$), liver metastasis ($p < 0.001$), bone metastasis ($p < 0.001$), adrenal gland metastasis ($p = 0.028$), and response to initial therapy ($p < 0.001$).

The OS also significantly associated with laboratory markers, including hypoalbuminemia < 35 g/l ($p = 0.044$), hyponatraemia <131 mmol/l ($p = 0.041$), and alkaline phosphatase ≥ 129 U/l ($p < 0.001$). On multivariate analysis, staging was confirmed as an independent prognostic factor of OS, HR 2.7 ($p = 0.022$), as was elevated alkaline phosphatase, HR 3.3 ($p = 0.004$).

The Manchester Score, which comprises laboratory values of lactate dehydrogenase, serum sodium, alkaline phosphatase and serum bicarbonate plus tumour stage and Karnofsky performance status was the only published scoring system of the 7 evaluated that showed a significant association with OS; patients placed in good, intermediate and poor prognosis groups using the Manchester Score had median OS of 12.9, 6.6 and 5.8 months, respectively ($p = 0.008$). Rothschild *et al.* Abstract 92P.

Practice point and future research opportunities

Although treatment decisions in SCLC are largely based on the extent of the disease, the outcome often differs among patients with the same stage disease, making other means of indicating outcomes useful in making a decision for treatment. Several prognostic scores have been recently advanced but few have been validated in independent patient populations. This study showed that overall survival was significantly associated with several clinical parameters and laboratory values, as well as the prognosis determined using the Manchester score. These findings confirm the prognostic value of the Manchester Score in an independent patient population of patients with SCLC.

EARLY STAGE NON-SMALL CELL LUNG CANCER

Possibility for overtreatment in clinically diagnosed early stage lung cancer raised

Lead author Talha Shaikh, Department of Radiation Oncology, Fox Chase Cancer Centre, Philadelphia, USA pointed out that, although diagnosis of early stage lung cancer is most often made by pathology in patients treated with radiotherapy, pathologic diagnosis was often difficult and could be complicated by the location of the tumour, the patient's medical comorbidities, or by patient preference. Results were reported from a review of data contained in the Surveillance, Epidemiology, and End Results (SEER) registry over an 8-year period beginning in 2004 to determine trends in clinical diagnosis of early stage lung cancer and the association between mode of diagnosis and treatment outcomes. This analysis included data from 7050 patients aged 18 years and older receiving only radiation therapy for stage I, clinical T1a-T2a lung cancer. The association between patient outcomes of overall survival (OS) were determined by Cox proportional hazards model and competing risk regression analysis was used to assess cancer specific survival (CSS) with each type of diagnosis and subsequent radiotherapy treatment.

No significant change over the course of the study was observed between the diagnostic methods used (p = 0.172): Pathological diagnosis was made in 6399 (90.8%) patients compared with 651 (9.2 %) patients who were clinically diagnosed.

Patients with clinically diagnosed disease demonstrated improved CSS outcomes that were significant in some patient subgroups. By multivariable analysis, improved CSS associated with clinical diagnosis, HR 0.82; 95% CI 0.71, 0.96. In patients stratified by clinical tumour stage, improved CSS was observed in clinically diagnosed T1a patients, HR 0.75; 95% CI 0.58, 0.96 (p = 0.022) and in patients with clinically diagnosed T1b tumours, HR 0.74; 95% CI 0.55,1.00 (p = 0.052). A stepwise increase in the hazard ratio (HR) for CSS according to T-stage and tumour size was seen when comparing clinically diagnosed versus pathologically diagnosed tumours. When outcome in the patients in the clinical diagnosis cohort was evaluated according to interval quartile tumour size, improved CSS was seen in patients with smaller (0 to 1.9 cm) tumours, HR 0.74; 95% CI 0.58, 0.99; (p = 0.040) and a trend towards improved CSS was seen in patients with tumours sized 2.0 to 2.7 cm, HR 0.78; 95% CI 0.58, 1.03 (p = 0.083).

However, clinically diagnosed early stage lung cancer did not associate with overall survival, HR 1.01; 95% CI 0.90,1.13. The authors concluded that the improved CSS seen in clinically diagnosed patients suggests possible overtreatment of benign disease, particularly in patients with smaller tumours. They advised that prudent patient selection is necessary to reduce the potential for overtreatment. Shaikh *et al.* Abstract 97O.

Practice point and future research opportunities

This analysis shows that far fewer patients over an 8-year period received a clinical rather than a pathological diagnosis of early stage lung cancer and improved rates of cancer specific survival but not overall survival were linked to a clinical diagnosis. It

also raised the possibility of overtreatment in clinically diagnosed patients with benign disease, paticulary those having small tumours.

However, using stereotactic ablative radiotherapy (SABR) as an example, overlapping outcomes between biopsy-proven and non-histologically-diagnosed lung cancer patients undergoing SABR have been recently reported. Also, the literature shows that a histological diagnosis is missing in from 8% to 100% of patients prior to SABR depending on cardiopulmonary function and the possibility of acute and chronic toxicities in compromised patients.

This retrospective analysis used the SEER registry, which does not include data on comorbidities, performance status, margin status, radiation dose, or chemotherapy use. Serious propensity score analysis in this context is difficult. It would be informative to know whether acute and chronic toxicities were reported in non-histologically diagnosed patients undergoing SABR, as would CSS results from SABR treated patients with peripheral versus central tumours. The 17-month median follow-up may be too brief to draw definitive conclusions and there is a need for critical review of manuscripts reporting outcomes of SABR in a mixed population (diagnosed and non-diagnosed), possibly focusing on histologically proven patients. The implications of cancer specific survival in clinical practice should be further evaluated.

Characterisation of tumour infiltrating lymphocytes in resectable early stage NSCLC

Sean R.R. Hall, Inselspital in Bern, Switzerland and colleagues questioned why many patients with non-small cell lung cancer (NSCLC) and documented PD-L1 expression fail to respond to blockade of the programmed cell death 1: programmed cell death ligand 1 (PD-1: PD-L1) pathway by characterising alterations in and the immunophenotype of the tumour infiltrating lymphocytes (TILs) in early stage NSCLC.

The investigators evaluated differences in TILs between tumour and matched normal samples obtained from 66 patients with histologically confirmed adenocarcinoma and squamous cell carcinoma. The samples were digested to single cell suspensions and multiparametre flow cytometry was used to detect simultaneous expression of a panel of fluorescently conjugated monoclonal antibodies directed at CD19, CD45RO, CD3, CD4, CD8, CD107a, PD-1, and CD127.

The 33 adenocarcinoma samples revealed a tumour compartment with enhanced infiltration of $CD4^+$ T cells ($p = 0.026$) together with a decrease in tumour infiltrating $CD8^+$ T cells ($p = 0.06$) compared to uninvolved tissue, which was not found in 33 squamous cell carcinoma samples. Cytotoxic degranulating CD4+ and CD8+ TILs based on a $CD107a^{hi}PD1^{lo}$ phenotype were significantly reduced in the tumor compartment in both histologies; the majority of TILs were $CD107a^{lo}PD1^{hi}$ ($p < 0.0001$). The $CD107a^{lo}PD1^{hi}$ phenotype in the squamous cell carcinoma samples associated with a decreased expression of CD127, a key molecule necessary for T cell homeostasis and survival, in both CD4+ ($p = 0.05$) and CD8+ TILs ($p < 0.0001$). However, decreased CD127 expression was found only on

CD8+CD107a^{lo}PD1^{hi} TILs in adenocarcinoma samples (p = 0.048). Hall *et al.* Abstract 98O.

Practice point and future research opportunities

This analysis provides evidence of T cell exhaustion in the tumour compartment in resectable early stage adenocarcinoma and squamous cell carcinoma. Further study is required to determine the functional significance on tumour specific T cell immunity and whether this plays a role in immune escape mechanisms via PD-1/PD-L1 pathway.

LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

Patient characteristics, not the type of chemotherapy, increases risk for the development of brain metastases in NSCLC

Lisa Hendriks, Maastricht University Medical Center, Maastricht, Netherlands and colleagues conducted this retrospective multicentre study of data from all consecutive patients with stage III non-small cell lung cancer (NSCLC) who completed chemoradiation (CRT). The primary endpoints were the development of brain metastasis within the 1st year and whether this was the only site of first relapse. Differences between regimens were assessed by a logistic regression model using known risk factors, including age, gender, histology, tumour, and node status. The analysis also evaluated the specific chemotherapy comprising the CRT regimen.

Between January 2006 and June 2014, a total of 737 patients underwent concurrent CRT (cCRT) and 101 patients had sequential CRT (sCRT); of these patients, 11% developed brain metastasis within a year and 5% had brain metastasis as only site of first relapse. Patients developing brain metastasis were significantly younger than those who did not; the mean age was 59 versus 63 years ($p < 0.001$), respectively. More, (49%) patients with brain metastasis were female, compared with 35% of patients with no brain metastasis ($p = 0.009$) and 51% of patients developing brain metastasis had primary disease of adenocarcinoma histology whereas this histology occurred in 37% of patients without brain metastasis ($p < 0.001$).

However, the type of treatment was not a factor of the development of brain metastasis. In 346 patients receiving high dose cCRT and 391 patients treated by low dose cisplatin monotherapy (LDC), brain metastases were detected in 11% of each cohort within one year of the diagnosis of stage III NSCLC ($p = 0.927$). The brain was the only site of first relapse for 4% of high dose cCRT and 5% of LDC patients ($p = 0.399$). The type of chemotherapy used as part of the CRT treatment did not affect the development of brain metastasis, which occurred in 11% of patients receiving cCRT and in 10% of patients receiving sCRT ($p = 0.834$). The development of brain metastases within one year, and brain metastases as the only site of first relapse were unaffected by whether cCRT or sCRT was used, OR 0.87 ($p = 0.695$) and OR 0.89 ($p = 0.838$), respectively. The brain was the only site of first relapse for 5% of cCRT and 4% of sCRT patients ($p = 0.724$). Similar results were reported regarding the development of brain metastasis and for brain metastasis as the site of first relapse in the comparisons of LDC versus high dose cCRT, OR 0.96 ($p = 0.861$) and OR 1.36 ($p = 0.404$), respectively. No differences were found between the impact of LDC versus high dose non-taxane and high dose taxane regimens and for LDC versus cisplatin/etoposide, cisplatin/vinorelbin, or weekly cisplatin/docetaxel. Hendriks. *et al.* Abstract 115PD.

Practice point and future research opportunities

Approximately 10% of patients develop brain metastases within the first year following a diagnosis of stage III NSCLC; the findings from this study suggest that this is independent of the type of chemotherapy used in a CRT regimen. Only age,

gender, and adenocarcinoma as the histology of NSCLC emerged as risk factors for the development of brain metastasis in this analysis.

PD-L1 expression as prognostic factor for survival after chemoradiotherapy of locally advanced NSCLC

In order to determine the possible clinical significance of PD-L1 expression, Martina Vrankar, Department of Radiotherapy, Institute of Oncology Ljubljana, Ljubljana, Slovenia and colleagues assayed tumour samples from 107 patients with inoperable locally advanced non-small cell lung cancer (NSCLC) who underwent concurrent chemoradiotherapy in their institution from 2005 to 2010 and evaluated the association between expression and treatment outcome. PD-L1 expression was assessed by immunohistochemistry (IHC) with rabbit monoclonal antibody SP142 (Ventana, USA), using a cutoff value of 5% stained cells as positive.

The study comprised samples from 36 male and 8 female patients who underwent combined chemoradiotherapy and had sufficient tissue for IHC. PD-L1 was expressed in 7 tumours obtained from 6 male and one female patients. Patient characteristics, including age, smoking status and gender, did not differ significantly according to PD-L1 expression. However, treatment varied by PD-L1 expression: A significantly greater proportion of patients with PD-L1 negative tumours completed radical irradiation with doses of ≥ 60 Gy compared to PD-L1 positive patients ($p = 0.018$). Furthermore, patients with PD-L1 positive tumours required a significantly lower dose intensity of concurrent chemotherapy with cisplatin (32.1%) and etoposide (40.0%) versus 40.0% and 80.5%, respectively, for PD-L1 negative patients.

PD-L expression significantly impacted survival: No patients demonstrating PD-L1 expression were alive at a median follow-up of 92.3 months, whereas 10 patients not expressing PD-L1 were still living. Median progression-free survival (PFS) was 19.9 months in patients negative versus 10.1 months in patients positive for PD-L1 expression ($p = 0.008$). Median overall survival (OS) was 28.0 versus 12.0 months for PD-L1 negative and PD-L1 positive patients, respectively ($p = .010$). Vrankar *et al.* Abstract 118P.

Practice point and future research opportunities

The standard treatment for inoperable locally advanced NSCLC includes concurrent or sequential chemotherapy and radiation therapy, which demonstrates long term survival rates in the order of 15%, making the investigation of new treatment strategies a priority. Immunotherapy is promising in this setting. These findings showed patients with tumours that were positive for PD-L1 expression had shorter median PFS and OS following concurrent chemoradiotherapy. This study is limited by small number of patients with tissue for IHC testing; therefore, no firm conclusions can be made but further investigation is warranted.

ADVANCED NON-SMALL CELL LUNG CANCER

Investigational agent BI 1482694 demonstrates robust, rapid response in patients with T790M mutation-positive NSCLC

Jin Soo Kim, Seoul National University, Seoul, South Korea presented results on behalf of colleagues from an extension trial evaluating BI 1482694 at the recommended phase II (RP2) dose. BI 1482694 is a novel, third-generation, oral EGFR tyrosine kinase inhibitor (TKI) that specifically targets tumours harbouring T790M mutations. The original trial enrolled patients with advanced EGFR mutation-positive non-small cell lung cancer (NSCLC) that were previously treated with EGFR-TKIs. Patients receiving additional lines of systemic therapy were also eligible. The maximum tolerated dose of 800 mg/day was taken forward for evaluation in the trial, wherein all 76 patients were required to have a documented T790M mutation.

At data cut-off of 30 June, 2015 data from 69 patients were evaluable for response evaluation; 44 (58%) patients were female, 61 (80%) had ECOG performance status (PS) ≤1, and 57 (75%) had received two or more lines of systemic therapy. The duration of BI 1482694 treatment was from 0.3 to 9.0 months, with 46 patients continuing BI 1482694. The objective response rate (ORR) by independent assessment was 62%; of these patients, 27 (84%) demonstrated response by treatment cycle 2. The ORR was similar among patients receiving either an EGFR TKI or chemotherapy as the last treatment before study entry. Tumour response was confirmed in 46% of patients and the disease control rate was 91% following BI 1482694 therapy.

The most commonly reported treatment-related adverse events (TRAEs) included diarrhoea, occurring in 55% of patients, nausea in 37%, rash in 38%, and pruritis, which occurred in 36% of patients. Grade 3 rash and pruritis were reported by 5% and 1% of patients, respectively. Treatment discontinuation due to a TRAE occurred in 3 (4%) patients and 9 (12%) patients reported serious TRAEs. No cases of QT prolongation syndrome or hyperglycaemia were reported. The authors announced that ELUXA 1, a global phase II trial evaluating the efficacy and safety of BI 1482694 in T790M-positive NSCLC is ongoing. NCT01588145 Park *et al.* Abstract 130O

Practice point and future research opportunities

The US Federal Drug Administration (FDA) has granted Breakthrough Therapy Designation for BI 1482694 in patients with NSCLC who have stopped responding to EGFR-TKIs. BI 1482694 was specificaly designed to target tumours with T790M mutation, which is the most common resistance mechanism developing in response to treatment with EGFR TKIs and occurs in approximately 50% to 60% of EGFR-TKI treated patients. BI 1482694 at the RP2 dose of 800 mg/day has shown meaningful clinical activity and a favourable safety profile. These data support BI 1482694 as a potential therapy for NSCLC patients resistant to first or second generation EGFR targeting agents.

Patient outcome improved with first-line gefitinib in EGFR-mutated advanced lung adenocarcinoma

Baohui Han, Shanghai Chest Hospital, Shanghai, China and colleagues randomised 121 previously untreated patients with advanced lung adenocarcinoma and EGFR sensitising mutations to receive combination chemotherapy plus gefitinib (group A), chemotherapy only (group B), or gefitinib monotherapy (group C). Chemotherapy in groups A and B comprised pemetrexed at 500 mg/m^2 plus carboplatin at AUC 5 and gefitinib was administered at 250 mg/day in groups A and C. All treatments were agiven until disease progression, unacceptable toxicity, or death occurred.

Treatment-naive patients with advanced lung carcinoma and EGFR mutations known to make tumours sensitive to tyrosine kinase inhibitors (TKIs) fared better with gefitinib, administered either with chemotherapy or as monotherapy, than similar patients receiving combination chemotherapy. The trial's primary endpoint, progression-free survival (PFS) was met: Median PFS for patients receiving combined chemotherapy plus gefitinib was 18.83 months (95% CI 16.82, 20.83) versus 5.75 months (95% CI 5.19, 6.31) with combined chemotherapy only, and versus 12 months (95% CI 9.90, 14.09) with sole gefitinib. With chemotherapy plus gefitinib, chemotherapy, and gefitinib the 6-month PFS was 92.5%, 42.5%, and 80.5%, respectively. The objective response rate (ORR) was 82.5%, versus 32.5%, and 65.9% in the respective treatment groups.

The most common adverse events (AEs) grades 3/4 were reported primarily in groups A and B and included neutropenia, fatigue, liver dysfunction, and skin allergy. Neutropenia occurred in 10.0% versus 12.5%, fatigue occurred in 7.5% versus 5.0% and skin allergy occurred in 10.0% versus 10% of patients, in groups A and B, respectively. Liver dysfunction was reported in 10% of group A patients and in 2.5% of patients in group C. NCT02148380. Han *et al.* Abstract 131O.

Practice point and future research opportunities

In this trial, gefitinib showed greater clinical benefit than chemotherapy when administered either with chemotherapy or as monotherapy to treatment-naive patients with advanced lung carcinoma and EGFR sensitising mutations. Gefitinib shows promise to become the new standard of care in advanced lung adenocarcinoma but these results must be confirmed in a larger trial.

Increased necitumumab benefit observed in patients with NSCLC and EGFR positive tumours: Results of a subgroup analysis of SQUIRE

Lead investigator Luis Paz-Ares of the Hospital Universitario Doce de Octubre in Madrid, Spain presented results from a subgroup analysis of patients with EGFR-expressing tumours participating in the phase III SQUIRE trial of combined necitumumab/chemotherapy versus sole chemotherapy. Necitumumab is a novel monoclonal antibody targeting EGFR. SQUIRE randomised patients with pathologically confirmed stage IV squamous non-small cell lung cancer (NSCLC) 1:1 to receive first-line treatment with gemcitabine at 1250 mg/m^2 on days 1 and 8 plus cisplatin at 75 mg/m^2 on day 1, with or without necitumumab at 800 mg i.v. on days 1

and 8. The treatment cycle was 21 days for a maximum of 6 cycles, after which patients showing no progression were continued on necitumumab monotherapy until progressive disease or intolerable toxicity. Tissue collection was mandatory.

Among all patients in SQUIRE, median overall survival (OS) with necitumumab plus chemotherapy was 11.5 months compared with 9.9 months for patients receiving the gemcitabine-cisplatin regimen only, HR 0.84; 95% CI 0.74, 0.96 (p = 0.012). The 1-year OS rate was 47.7% versus 42.8%, and the 2-year OS rate was 19.9% compared with 16.5%, for the necitumumab and chemotherapy arms, respectively.

The pre-specified analysis reported at ELCC was from data of 982 patients with evaluable immunohistochemistry (IHC) assay results of EGFR protein expression. Patients were characterised as having tumours that were EGFR-expressing (EGFR>0) or non-expressing (EGFR=0). Baseline characteristics for EGFR>0 patients were well-balanced between the chemotherapy plus necitumumab and sole chemotherapy arms.

EGFR protein was found to be expressed by the tumours of nearly all patients (95.2%) and just 4.8% of patients had tumours without detectable EGFR protein. The analysis revealed that patients with EGFR expression receiving chemotherapy plus necitumumab had significantly improved OS, HR 0.79; 95% CI 0.69-0.92 (p = 0.002) and progression-free survival (PFS), HR 0.84; 95% CI 0.72, 0.97, compared with patients with EGFR expression receiving chemotherapy alone (p = 0.018). In patients with EGFR negative tumours, for the comparison of OS in the chemotherapy plus necitumumab arm versus chemotherapy arm, the HR was 1.52; 95% CI 0.74, 3.12 (p = 0.253) and for PFS, HR was 1.33; 95% CI 0.65, 2.70 (p = 0.428). The administeration of post-progression anticancer therapy was similar between arms at 49% versus 47 % of EGFR positive versus EGFR negative patients, respectively.

Adverse events grades ≥3 in EGFR positive patients receiving chemotherapy plus necitumumab having a >3% increase over sole chemotherapy were hypomagnesemia in 9.6% versus 0.9%, and skin rash in 6.4% versus 0.4% of EGFR positive and negative patients, respectively. NCT00981058. Paz-Ares *et al.* Abstract 132O.

Practice point and future research opportunities

These subgroup results are similar to those seen in the phase III SQUIRE trial where the addition of necitumumab, a novel anti-EGFR monoclonal antibody, significantly improved survival in patients with stage IV squamous NSCLC. The FDA Oncologic Drugs Advisory Committee and the European Medicines Agency (EMA) supported the approval of necitumumab in July 2015 as first-line treatment in combination with gemcitabine and cisplatin for patients with advanced squamous NSCLC based on these results.

In this analysis, the subgroup of patients whose tumours expressed EGFR experienced significantly prolonged overall survival when necitumumab was added to conventional chemotherapy. An overall survival benefit was observed across all pre-specified subgroups in patients with EGFR-expressing tumours. These findings respresent practice changing results that support the addition of necitumumab in

patients with squamous NSCLC, especially the majority of patients with EGFR-expressing tumours.

Plasma test detects EGFR T790M mutation in patients with EGFR mutation-positive advanced NSCLC

Suzanne Jenkins, AstraZeneca, Macclesfield, UK, and colleagues evaluated samples from the AURA extension and AURA2 trials of osimertinib to determine parametres that could aid in patient selection for this treatment. Osimertinib is an irreversible EGFR tyrosine kinase inhibitor (TKI) targeting the T790M EGFR-TKI resistance mutation and common EGFR-TKI-sensitive mutant forms of EGFR. Enrollment in either of the single-arm phase II registration studies was incumbent upon detection of the T790M mutation by the cobas® EGFR Mutation Test in formalin-fixed, paraffin-embedded tissue and in plasma samples using the cobas® EGFR Mutation Test v2.0. Next generation sequencing (NGS) analysis was also done on the plasma samples. Agreement (positive and negative) between the cobas tissue and the cobas plasma tests for detection of EGFR mutations was calculated in the pooled phase II analysis set, whereas agreement between the cobas plasma test and NGS analysis of plasma was calculated using samples from patients participating in AURA2.

The pooled analysis demonstrated positive percentage agreement (PPA) of 61.4% and negative percentage agreement (NPA) of 78.6% between the cobas tissue and plasma tests for detection of T790M. The analysis of AURA2 data showed PPA of 91.5% and NPA of 91.1% between the cobas plasma test and the NGS analysis of plasma. Common sensitising mutations were also analysed and showed PPA of 75.6% and NPA of 98.1% between the cobas tissue and plasma tests were, for the L858R mutation, and 85.1% and 98.0%, respectively, for exon 19 deletions.

The subset of patients with a positive T790M plasma test and all patients with a positive T790M cobas tissue test showed comparable objective response rates as of May 2015. NCT01802632 and NCT02094261. Jenkins *et al.* Abstract 134O.

Practice point and future research opportunities

The agreement between the plasma and tissue tests for detection of T790M suggests that approximately 60% of patients with T790M positive NSCLC could have avoided an invasive biopsy by using the plasma test. However, a tissue-based test is advised for EGFR-TKI-resistant patients, without detectable T790M in plasma, to address the potential for false negative results from the plasma test. The utility of both plasma- and tissue-based tests in the diagnostic setting is demonstrated in this study.

Biomarkers for osimertinib response identified in NSCLC

Lead author Geoffrey R Oxnard, Dana-Farber Cancer Institute, Boston, MA, USA and colleagues performed an analysis to determine whether genotyping of plasma DNA could identify patients most likely to obtain clinical benefit from osimertinib (AZD9291), an irreversible EGFR tyrosine kinase inhibitor (TKI) selective for the

EGFR mutations at exons 19 and 20 and the T790M mutation that confer resistance to first generation TKIs. Osimertinib has recently been approved by the FDA for the treatment of patients with EGFR T790M positive metastatic NSCLC who have progressed on EGFR-TKI therapy.

The analysis included patients with advanced non-small cell lung cancer (NSCLC) plus a common EGFR-sensitising mutation and T790M that was either central-lab confirmed in the tumour and/or by exploratory plasma genotyping. Patients had received 20 mg to 240 mg of osimertinib in the Phase I AURA trial.

Concordance for T790M was 70% in 216 patients with both plasma and tumour genotyping results, which improved to 80% when the analysis comprised only the 137 cases with a sensitising mutation that was detected in plasma.

As of the data cut-off of 1 May 2015, the objective response rate (ORR) was 62% in 179 patients having tumour-detected T790M versus 62% in 167 patients with plasma-detected T790M. Progression-free survival (PFS) was identical at 9.7 months in the respective cohorts. In the T790M negative cohort, the ORR was 26% in 58 patients undergoing tumour assessment versus 46% in 104 patients with T790M assessed in plasma; PFS in these groups was 3.4 months versus 8.2 months, respectively.

When the investigators used the detection of sensitising mutation in plasma as a control, they found that plasma T790M negative cases could be classified into a 'T790M undetected' group plus sensitising EGFR group and a 'plasma uninformative' groups. The T790M undetected/sensitising EGFR group had poorer outcomes following osimertinib treatment and demonstrated an ORR of 38% and PFS of just 4.4 months compared with the plasma uninformative group, which had an ORR of 64% and PFS of 15.2 months. NCT01802632. Oxnard *et al.* Abstract 135O.

Practice point and future research opportunities

Detection of biomarkers in plasma showed good concordance with biomarkers detected in the tumours of patients with NSCLC, paving the way for a non-invasive assay that may be used to identify patients likely to respond to osimertinib. These data support the investigation of a new paradigm for resistance management, with rapid plasma genotyping as a test option prior to undergoing a biopsy for T790M. For EGFR-TKI-resistant patients without detectable T790M in plasma, a tissue-based test is advised to identify T790M positive candidates for osimertinib therapy. Testing for a sensitising mutation in plasma may serve as a control for false negative plasma T790M results.

Osimertinib plus durvalumab demonstrates clinical activity but raises safety concerns in advanced NSCLC

Myung-Ju Ahn, Samsung Medical Center, Sungkyunkwan University, Seoul, Republic of Korea, presented results from the TATTON trial evaluating the efficacy and safety of the combination of osimertinib (AZD9291) plus durvalumab in patients with advanced non-small cell lung cancer (NSCLC). Osimertinib is an oral, potent,

irreversible, third-generation EGFR tyrosine kinase inhibitor (TKI) that selectively targets mutated EGFR and T790M resistance mutations and durvalumab (MEDI4736) is a high-affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to both PD-1 and CD80.

TATTON was a multi-arm trial conducted in two parts: Part A was a dose escalation study in patients with advanced lung cancer that had received prior treatment with an EGFR-TKI and had disease progression afterwards. Part B was a dose expansion trial conducted in patients with advanced disease that were EGFR-TKI treatment-naive and required to have had pre-study tumour biopsies for central determination of EGFR T790M status. In part A, osimertinib was administered at 80 mg orally once daily plus durvalumab at 3 mg/kg or 10 mg/kg i.v. two times weekly and patients received 80 mg daily of osimertinib plus 10 mg/kg by i.v. twice a week in part B. All patients had tumours with confirmed EGFR-mutant NSCLC and no contraindication for immunotherapy; patients with a history of interstitial lung disease (ILD) were excluded. The primary objectives of both study parts were safety and tolerability and the secondary objective was clinical activity of the combination.

Updated safety data from the osimertinib plus durvalumab arm of both parts of TATTON were reported. As of data cut-off, the osimertinib/durvalumab combination had been administered to 23 patients in part A and to 11 patients in part B. The most commonly reported all-causality adverse events of any grade in part A were nausea, reported by 39% of patients, vomiting by 39%, anaemia by 35%, and diarrhoea, which was reported by 35% of patients. In part B, 55% of patients reported diarrhoea and 45% reported nausea.

Adverse events reported by more than 3 patients at any dose in the osimertinib plus durvalumab combination arm of TATTON

Patients with an AE AE by preferred term, occurring in more than three patients at any dose	Part A				Part B	
	Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W (N=10)		Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=13)		Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=11)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Rash (grouped terms)	5	1	6	0	7	0
ILD (grouped terms)	2	1	4	1	7*	3
Diarrhoea	3	0	3	0	5	0
Pyrexia	2	0	2	0	4	0
Stomatitis	1	0	1	0	4	0
Nausea	3	0	5	0	3	0
Anaemia	4	0	4	1	1	0
Vomiting	7	1	2	0	0	0
Decreased appetite	3	1	4	0	1	0

*One patient reported ILD following 13 Nov 2015 data cut-off
Population: safety analysis set; data cut-off: 13 Nov 2015

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An increase in ILD events was reported with the combination of osimertinib plus durvalumab compared to that seen with either drug alone. ILD occurred in 6 (26%) patients in part A; of these, 2 cases were grades 3/4. ILD was reported by 7 (64%) patients in part B; of these, 3 cases were grades 3/4. No grade 5 cases of ILD occurred in either cohort and there were no fatalities; most patients were managed with corticosteroids. The median time from the beginning of treatment to ILD onset was 69 days. The authors pointed out that the rates of ILD (grouped terms) seen with osimertinib monotherapy and durvalumab monotherapy are 2.9%, with 14 cases at grades 3/4 and 4 cases at grade 5, and 2.0% with 6 cases at grades 3/4 and one grade 5 case, respectively. Although the combined ILD rate of 38% with 5 cases of grades 3/4 reported for the combination was much greater than either sole agent, there was no apparent increase in the severity of ILD.

An increase in ILD events was reported with the combination of osimertinib plus durvalumab compared to that seen with either drug alone, without an increase in severity

Part A	6/23 (26%)
Dose 1: Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W	2/10 (20%)
Dose 2: Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W	4/13 (31%)
Part B: Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W	7*/11 (64%)
Part A and Part B	13/34 (38%; 95% CI 18, 52)†

†5 events were Grade 3/4 and there were no fatalities; most cases were managed using steroids

Entire osimertinib clinical programme (Phase I and II)	
Osimertinib monotherapy	35/1207 (3%)
Durvalumab monotherapy	23/1149 (2%)

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*One patient reported ILD following 13 Nov 2015 data cut-off
TATTON Population: safety analysis set; data cut-off: 13 Nov 2015

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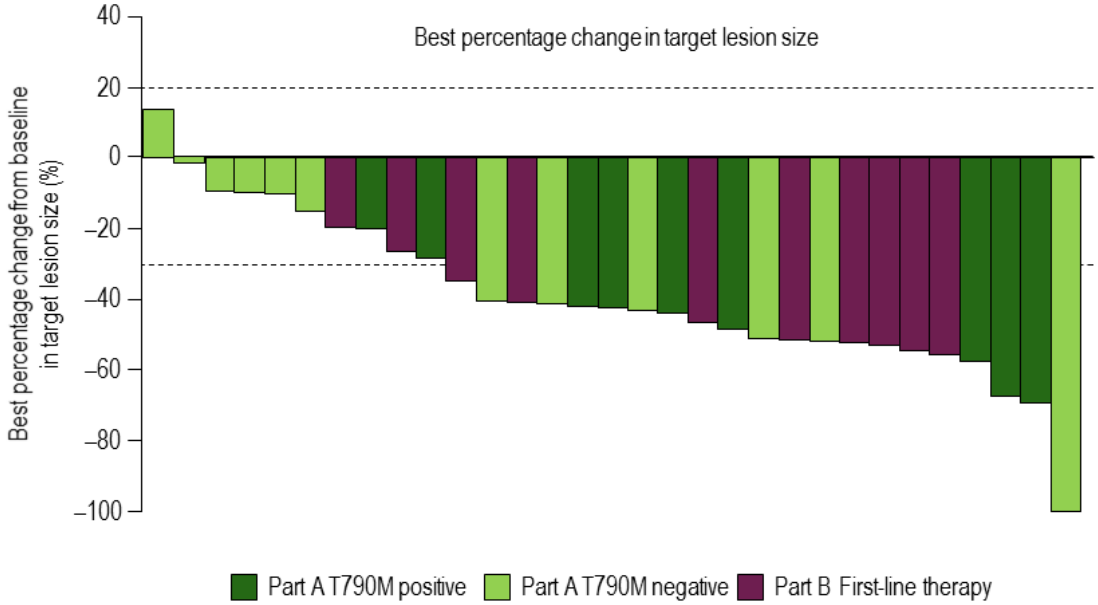
Promising clinical activity was demonstrated with the combination in patients with advanced disease. Data were evaluable for response in 21 part A patients: Partial response (PR) was achieved by 12 patients and 9 patients had confirmed PR. Stable disease (SD) was achieved by 9 patients. Of 10 patients with evaluable data from part B, 8 patients achieved PR, which was confirmed in 7 patients, and SD was observed in 2 patients.

Tumour response suggests encouraging clinical activity of osimertinib plus durvalumab in EGFRm NSCLC



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Population: evaluable for response set; data cut-off: 13 Nov 2015
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The osimertinib plus durvalumab treatment arm has currently been halted until the health profile of each as monotherapy has been more fully investigated. NCT02143466. Ahn *et al.* Abstract 136O.

Practice point and future research opportunities

Encouraging clinical activity was demonstrated by the combination of osimertinib plus durvalumab in patients with advanced NSCLC that had received prior treatment with an EGFR-TKI and also in EGFR-TKI naive patients that was offset by safety concerns over the occurrence of ILD in some patients.

Anti-PD-1/PD-L1 strategies are established second-line NSCLC treatment and show response rates of up to approximately 20%. Responses are durable, and translate into remarkable long-term survival. Toxicity in general is less than that experienced with chemotherapy treatment-related adverse findings from dual checkpoint inhibition. Combinations of a checkpoint inhibitor and TKI are under investigation and are challenging the field. In addition to this trial of durvalumab plus osimertinib in EGFR-mutated NSCLC, durvalumab is currently being investigated in combination with gefitinib in EGFR-mutated NSCLC. The several generations of EGFR-TKIs provide a strong standard therapy and PD-L1 expression seems to be upregulated in

early-stage EGFR mutation positive NSCLC. Clinical data in advanced disease, however, show lower response rates to anti-PD-1/PD-L1 therapies in EGFR mutated tumours. Furthermore, overlapping toxicities may occur. There is a clear rationale for immunotherapy/TKI combinations, but the toxicity experienced with treatment-related adverse events will be crucial.

In this study, an increase in ILD was reported with combined osimertinib and durvalumab compared to what would be expected with either drug alone. Although the combined ILD rate of 38% with 5 cases of grades 3/4 reported for the combination was much greater than either sole agent, there was no apparent increase in the severity of ILD. The tumour response rate suggests encouraging clinical activity of this combination in EGFR-mutant NSCLC, especially in patients with prior EGFR-TKI therapy. Enrollment to the combination arm of the TATTON has been suspended; this does not impact upon the other arms of the TATTON, nor on osimertinib and durvalumab as monotherapies, or in other combinations.

High baseline cytokine levels may serve as a biomarker of greater nivolumab efficacy in advanced platinum-refractory squamous NSCLC

Suresh Ramalingam of the Winship Cancer Institute at Emory University in Atlanta, USA, reported the results on behalf of colleagues of an evaluation of baseline serum cytokines in nivolumab-treated patients. Nivolumab was administered in the phase II CheckMate 063 trial at 3 mg/kg Q2W to 117 patients until progressive disease or unacceptable toxicity occurred. The phase III CheckMate 017 trial randomised 135 patients to receive nivolumab at the same dose and 137 patients to docetaxel at 75 mg/m^2 Q3W until progressive disease (PD) or discontinuation due to toxicity or other reasons. The primary endpoints were objective response rate (ORR) by RECIST v1.1 and overall survival (OS) in CheckMate 063 and CheckMate 017, respectively. Treatment beyond PD was permitted in both studies.

Key efficacy and safety parametres were similar at a 2-year follow-up in both CheckMate trials. With nivolumab, the two-year OS rate in CheckMate 063 was 22% (95% CI 15, 30) and median OS was 8.1 months (95% CI 6.1, 10.9). Overall, 75% of CheckMate 063 patients experienced a treatment-related adverse event (TRAE) of any grade and 17% of patients experienced grade 3/4 TRAEs; 12 % of patients discontinued nivolumab due to a TRAE and death occurred in 2 patients that was determined as treatment-related.

In CheckMate 017, the 12-month OS rates of nivolumab compared to docetaxel were 42% (95% CI 33.8%, 50.4%) versus 24% (95% CI 17.4%, 31.7%) and the 18-month OS rates were 28% (95% CI 20.8%, 35.8%) versus 13% (95% CI 7.6%, 18.6%), respectively. Median OS was 9.2 months with nivolumab (95% CI 7.33, 12.62 months) versus 6.0 months with docetaxel (95% CI 5.29, 7.39 months). The ORR with nivolumab was 20% (95% CI 14%, 28%) versus 9% with docetaxel (95% CI 5%, 15%).

Of the 131 nivolumab treated patients and 129 docetaxel patients in CheckMate 017, TRAEs of any grade occurred in 59% versus 87% of patients, respectively, experienced a TRAE of any grade and 8% versus 56% of patients in the respective groups experienced grade 3/4 TRAEs. Study discontinuation due to a TRAE was reported for 5% of nivolumab versus 10% of docetaxel patients. No treatment-related

deaths occurred with nivolumab and 2 deaths occurred in patients receiving docetaxel that were determined treatment-related.

A multivariate exploratory analysis done on the levels of baseline serum cytokines in 222 of nivolumab-treated patients participating in either trial generated a SQ-cytoscore, defined as “high” or “low” based on the median cut-off, which allowed quantification of the effect of the identified cytokine set on OS. This analysis showed that 102 patients in both trials having a high SQ-cytoscore achieved OS nearly 3 times longer than 120 patients having a low SQ-cytoscore; median OS was 15.6 versus 5.3 months, HR 0.48; 95% CI 0.36, 0.64) in the high and low score groups, respectively ($p < 0.0001$). CheckMate 063 (NCT01721759) CheckMate 017 (NCT01642004). Lena *et al.* Abstract 137O.

Practice point and future research opportunities

Patients with platinum refractory, advanced squamous non-small cell lung cancer (NSCLC) had few treatment options until nivolumab was approved in both the United States and the European Union based on a survival advantage over docetaxel that was demonstrated in CheckMate 017. Squamous cell NSCLC is a different and difficult disease in comparison to the non-squamous adenocarcinoma type of NSCLC. In terms of patient demographics, non-squamous adenocarcinoma NSCLC is the most common cell type in women and non-smokers and patients tend to be younger. Squamous NSCLC is the most common histology in men, has a stronger association with smoking, and patients tend to be slightly older. In terms of localisation, non-squamous adenocarcinoma NSCLC is peripheral, while squamous is central, and may be more likely to result in blood vessel haemorrhages. Cavitation is not typical in non-squamous adenocarcinoma, while it is typical in squamous NSCLC. In non-squamous adenocarcinoma, patients often present with metastatic disease before symptom development, while squamous NSCLC is more likely to be detected at a localised stage due to earlier onset of symptoms. Brain metastases are more common in non-squamous adenocarcinoma, while regional lymph nodes, adrenal glands, bone, liver, and brain are the sites of metastases in squamous. Pathology also differs: Adenocarcinoma is characterised by the presence of glands and papillary structures, neoplastic cells with round to oval nuclei, prominent nucleoli, and moderate amounts of cytoplasm, staining for mucin, TTF-1, and cytokeratin 7, whereas squamous NSCLC presents a flattened appearance, intercellular bridges, individual cell keratinisation, keratin pearls, staining for p63, p40, cytokeratin 5/6 and few treatable oncogenic alterations.

Further analysis of data from these trials showed that baseline serum cytokine levels altered the efficacy of immunotherapy with nivolumab in platinum pretreated patients with advanced squamous NSCLC, suggesting that these levels may be indicators of patient outcome following nivolumab. The SQ-cytoscore appears to be associated with better prognosis in patients with advance squamous NSCLC; however, these preliminary SQ-cytoscore findings require prospective validation.

Recent gains in survival have been greater in stage IV adenocarcinoma versus squamous NSCLC, with significantly increased survival reported for patients diagnosed between 2002 to 2005 with adenocarcinoma compared with those diagnosed with squamous cell carcinoma. Survival has been improving since 1990

for NSCLC of all histologies; while second-line treatment for squamous cell carcinoma was not really a model for long term overall survival, it has changed recently.

As predictors of outcome in squamous cell carcinoma clinical factors are not suitable and PD-L1 expression is not helpful. However, in the CheckMate trials, a high SQ-cytoscore served as a prognostic factor and these patients showed longer overall survival. But the association of dynamic changes in cytokine levels with the efficacy of checkpoint inhibitors may not be the best marker and circulating immune cells may be a marker of interest. It would be interesting to know if the cytoscore held the same prognostic ability in non-squamous NSCLC. There is a possibility for long-term survival with checkpoint-inhibitors, but we are still on the way to identifying the patients who will benefit.

These results confirm the efficacy of nivolumab at two years in patients with advanced squamous NSCLC.

Afatinib dose reduction decreases adverse events without altering efficacy in NSCLC

Lead author Martin Schuler, University Hospital Essen in Essen, Germany discussed this analysis, which included data from 229 patients treated with afatinib in LUX-Lung 3 and 239 afatinib-treated patients in LUX-Lung 6. In both trials, patients experiencing drug-related grade 3 or selected prolonged grade 2 adverse events (AEs) could have the approved 40 mg dose of afatinib reduced in 10 mg decrements to a 20 mg minimum dose. The investigators evaluated the incidence and severity of commonly reported AEs occurring before and after dose reduction. The AEs, pharmacokinetics (PK) and progression-free survival (PFS) were compared between patients having dose reduction to 30 mg with patients receiving afatinib at 40 mg participating in the two trials.

Dose reductions to 30 mg were administered to 122 (53%) and 67 (28%) of afatinib treated patients in LUX-Lung 3 and 6, respectively. Most, 86% and 82%, dose reductions in the respective trials were made within the first 6 months of treatment. Analysis of combined PK data from both trials suggested that dose reduction was more likely to occur in patients having higher plasma concentrations of afatinib: The geometric mean plasma afatinib concentration on day 43 was 23.3 ng/mL plasma in 59 patients receiving dose reduction compared with 22.8 ng/mL in 284 patients remaining at the 40 mg dose. Median PFS was similar among patients receiving a dose reduction during the first 6 months of treatment compared with patients remaining at the 40 mg dose in both trials. PFS was 11.3 months compared with 11.0 months (hazard ratio [HR] 1.25; 95% CI 0.91, 1.72) in LUX-Lung 3 and 12.3 versus 11.0 months (HR 1.00; 95% CI 0.69, 1.46) in LUX-Lung 6 in patients receiving 30 mg and 40 mg afatinib, respectively.

Patients in both trials receiving dose reductions experienced a decrease in the incidence and severity of treatment-related AEs, including diarrhoea, stomatitis and rash or acne of grade 3 or greater severity; before dose reduction these AEs occurred in 20.5%, 12.3%, and 26.2% of patients in LUX-Lung 3 and in 11.9%,

13.4%, and 38.8% of patients in the LUX-Lung 6 trial, respectively. Following dose reduction, the incidence of grade 3 or greater diarrhoea, stomatitis and rash or acne was 4.1%, 0, and 3.3% versus 0, 15%, and 4.5% in LUX-Lung 3 and 6, respectively. NCT00949650 and NCT01121393. Schuler *et al.* Abstract 138PD.

Practice point and future research opportunities

Afatinib may be adjusted from the approved 40 mg per day dose according to individual tolerability without compromising clinical benefit in patients with advanced EGFR mutation-positive non-small cell lung cancer (NSCLC). Findings from this post-hoc analysis of data from the LUX-Lung 3 and 6 trials suggest that dose reductions occurred most often in patients having higher plasma concentrations of afatinib.

Lifetime incidence of brain metastases in EGFR-mutant lung cancer treated with first-line EGFR TKIs

D. Z. Ng of the Yong Loo Lin School of Medicine, National University of Singapore, Singapore noted the common occurrence of brain metastases in EGFR mutation-positive non-small cell lung cancer (NSCLC). Together with colleagues, he reviewed data from 211 patients diagnosed with advanced EGFR mutation-positive lung adenocarcinoma between August 2009 and February 2013. The patients mostly had exon 19 or 21 mutations and were treated with 1st line EGFR tyrosine kinase inhibitors (TKIs). Patient demographics, presence/absence of brain metastasis at initial diagnosis, pattern of relapse, type of mutation, and choice of EGFR TKI were evaluated and brain metastases-free survival (BMFS) was estimated using the Kaplan-Meier method. Factors associated with risk for the development of brain metastases were determined by univariate and multivariate Cox regression analyses.

Brain metastases were present at baseline in 63 (29.9%) patients, not present in 137 patients, and data were missing for 11 patients. In the cohort without baseline brain metastases, 84 (61.3%) patients were female, 116 (84.7%) were Chinese, 108 (78.8%) never-smokers, and the median age was 65 (range: 40 to 84) years. First-line treatments included gefitinib in 89.8% of patients, erlotinib in 4.4%, and afatinib in 5.8% of patients.

The median follow-up was 31.3 months during which 40 (29.2%) patients developed brain metastases; of these 15 (37.5%) patients showed brain metastases during first-line TKI treatment. Of the 25 patients developing brain metastases after first-line TKI, 14 had received further TKI therapy beyond first-line. The cumulative incidence rate of brain metastases (CIBM) at 24 months was 29.2% (95% CI 21.3, 39.3). On multivariate analysis, the presence of liver metastases at diagnosis (HR 2.76; 95% CI 1.25, 6.10) emerged as the strongest predictive factor for BMFS. Among patients showing first progression in non-CNS sites, there was no significant difference in time to development of brain metastases after disease progression between the 23 of 76 patients who received TKI beyond progression and the one patient of 21 that did not (p = 0.123). In this analysis, the lifetime incidence of brain metastases in EGFR mutation positive lung adenocarcinoma was 48.8% in patients receiving first-

line TKI treatment. In patients without baseline brain metastases, the CIBM at 12 and 24 months was 13.7% and 29.2%, respectively. Ng *et al.* Abstract 139PD.

Practice point and future research opportunities

This analysis determined the lifetime incidence of brain metastases in patients with EGFR mutation-positive lung adenocarcinoma that were treated with first-line EGFR TKIs, the likelihood of brain metastases development while on EGFR TKI treatment, and identified the presence of liver metastases at the time of diagnosis as a risk factor for development of brain metastases. The study is limited by a small sample size of predominantly the same ethnicity, making analysis in a larger, more varied population necessary to support these conclusions.

Afatinib outperforms gefitinib in treatment-naive patients with NSCLC and EGFR mutation: LUX-Lung trial results

Keunchil Park, Samsung Medical Center, Sungkyunkwan University School of Medicine, South Korea presented findings on behalf of colleagues from the LUX-Lung trial, a direct comparison of afatinib versus gefitinib as first line treatment of patients with stage IIIB/IV non-small cell lung cancer (NSCLC) and confirmed EGFR Del19 or L858R mutations. Patients were stratified by mutation type and the presence or absence of brain metastases; 160 patients were randomised to 40 mg afatinib and 159 patients to 250 mg gefitinib until radiological disease progression and beyond by investigator decision. The 3 co-primary endpoints were progression-free survival (PFS) by independent review, time to treatment failure (TTF) and overall survival (OS). Secondary endpoints included objective response rate (ORR), disease control rate, tumour shrinkage and safety.

Baseline characteristics were balanced in treatment arms regarding race and mutation status; 58.8% versus 55.3% of patients were Asian and 57.5% versus 58.5% of patients harboured EGFR Del19 in the afatinib versus gefitinib arms, respectively. Fewer patients (56.9%) were female in the afatinib arm compared with 66.7% in the gefitinib arm.

Patients showed significantly improved PFS with afatinib over gefitinib, HR 0.73; 95% CI 0.57, 0.95 ($p = 0.017$) that was consistent across subgroups of mutation type and race. TTF was also significantly improved with afatinib versus gefitinib, HR 0.73; 95% CI 0.58, 0.92 ($p = 0.007$). The independently assessed ORR was 70% with afatinib compared to 56% with gefitinib ($p = 0.008$). OS data were not mature.

No unexpected short- or long-term treatment-related toxicities occurred in either study arm. Commonly reported grade ≥3 related adverse events (AEs) with afatinib were diarrhoea in 12.5% and rash/acne in 9.4% of patients and 8.3% of gefitinib patients had increased alanine aminotransferase. Drug-related interstitial lung disease was reported for 4 (2.5%) gefitinib patients whereas this did not occur in the afatinib arm. Discontinuation due to drug-related AEs was 6.3% in each arm. NCT01466660. Park *et al.* Abstract 140PD.

Practice point and future research opportunities

First-line treatment with afatinib significantly improved progression-free survival, objective response rate, and time to treatment failure over gefitinib in patients with EGFR mutation positive advanced non NSCLC. The safety profile showed both drugs were tolerable and few patients discontinued due to adverse events. The overall survival data are anticipated.

Novel brigatinib demonstrates efficacy in patients with ALK-positive NSCLC

Rafael Rosell, Medical Oncology Service, Catalan Institute of Oncology, Barcelona, Spain presented early findings on behalf of colleagues from this ongoing phase I/II trial of brigatinib, an investigational oral tyrosine kinase inhibitor (TKI) that has demonstrated preclinical activity against the oncogenic ALK fusion protein and other mutations that display crizotinib resistance. The single-arm, open-label, multicentre study enrolled 137 patients with advanced malignancies that were administered brigatinib at 30 to 300 mg total daily.

Efficacy per RECIST v1.1 in the cohort of patients with ALK-positive non-small cell lung cancer (NSCLC) and overall safety as of February 17, 2015 were reported at ELCC. In the ALK-positive NSCLC cohort of 78 patients, the median age was 54 (range: 29 to 83) years, 49% of patients were female, and 90% had received prior crizotinib. At data cut-off, 45 (57%) patients remained on study and the median time on brigatinib was 12.6 months (range: 1 day to 35.5 months). The objective response rate (ORR) was 71% in 70 ALK-positive NSCLC patients that had received prior crizotinib (95% CI 59, 82); complete response (CR) was achieved by 4 (6%) patients, partial response (PR) by 46 (66%), 11 (16%) had stable disease (SD) and 6 (9%) patients experienced progressive disease. In 8 crizotinib-naive patients, the ORR was 100% with 3 (38%) CR and 5 (63%) PR. The median duration of response was 9.9 versus not reached, and the median progression-free survival (PFS) was 13.4 months versus not reached in crizotinib-treated and crizotinib-naive patients, respectively.

As of February 9, 2015, a post hoc independent radiological review of patients showing brain metastases at baseline showed that 8 of 15 (53%) patients with measurable (≥10 mm) brain lesions had an intracranial response demonstrating an intracranial disease control rate of 87%; this response included 5 of 9 (56%) patients that had received no prior brain radiotherapy. In all, 19 patients showed an intracranial response lasting a median duration of 18.9 months.

Treatment-emergent adverse events (TEAEs) were mostly grades 1/2 and reported in ≥30% of all 137 patients, including nausea in 52% of patients, fatigue in 42%, diarrhoea in 40%, headache in 33%, and cough in 32% of patients. All-cause serious TEAEs occurring ≥2% of patients were dyspnoea in 7% of patients, pneumonia in 6%, hypoxia in 5%, pulmonary embolism in 3%, and pyrexia in 2% of patients. NCT01449461. Rosell *et al.* Abstract 133O.

Practice point and future research opportunities

Promising efficacy findings with brigatinib, an oral TKI with activity against the oncogenic ALK fusion protein and other mutations displaying crizotinib resistance, were reported in a cohort of patients with ALK-positive NSCLC. Brigatinib showed antitumour activity in both crizotinib-treated and crizotinib-naive patients, including those with brain metastases at baseline, where an intracranial response was also observed. Brigatinib demonstrated an acceptable safety profile in the overall study cohort of patients with ALK-positive and ALK-negative NSCLC. The efficacy results from the ALK-negative cohort are anticipated as are the findings from the randomised, phase II trial of brigatinib in patients with crizotinib-resistant ALK-positive NSCLC, which has completed accrual.

Ceritinib shows similar clinical benefit in the ASCEND-1 and -2 trials of crizotinib-pretreated patients with ALK-rearranged NSCLC and brain metastases

Enriqueta Felip, Vall d'Hebron University Hospital, Barcelona, Spain, discussed findings on behalf of colleagues from 2 trials of ceritinib, a selective oral ALK inhibitor that has shown a 20-fold greater potency than crizotinib in vitro. All enrolled patients had clinically/neurologically stable brain metastases upon enrollment. In both trials, patients received oral ceritinib at 750 mg per day. Computed tomography/magnetic resonance imaging (CT/MRI) scans were done at baseline and every 6 weeks in the phase I ASCEND-1 trial or every 8 weeks in the phase II ASCEND-2 trial. Efficacy analyses were done by Blinded Independent Review Committee (BIRC) in ASCEND-1 and whole body responses were assessed according to RECIST in ASCEND-2. Pooled intracranial responses were evaluated by BIRC, retrospectively in ASCEND-1 and prospectively in ASCEND-2. Of the 98 and 100 patients in the ASCEND-1 and -2 trials, respectively, 69.4% and 72.0% had received prior radiotherapy to the brain. Most patients had also received prior chemotherapy and all patients had received prior crizotinib. The primary objectives of both trials were efficacy and safety.

Patients demonstrated both whole body and intracranial responses to ceritinib: Regarding the intracranial response, a total of 61 patients in both trials had measurable lesions at baseline. Pooled data showed an overall intracranial response rate of 37.7% (95% CI 25.6%, 51.0%) and an intracranial disease control rate (DCR) of 73.8% (95% CI 60.9%, 84.2%). The median intracranial duration of response (DoR) was 12.8 (95% CI 6.9, NE) months.

In ASCEND-1, the median follow-up for 98 patients was 9.8 (range: 0.1 to 22.2) months. The overall response rate (ORR) was 41.8% (95% CI 31.9%, 52.2%) and the DCR was 69.4% (95% CI 59.3%, 78.3%). The median DoR was 8.2 (95% CI 5.6 to 13.1) months. Median progression-free survival (PFS) was 6.7 (95% CI 5.4, 9.5) months. In ASCEND-2, median follow-up for 100 patients was 11.2 (range: 0.2 to18.9) months. Although the ORR was lower at 32% (95% CI 23.0%, 42.1%) months, DCR and and median PFS were similar to ASCEND-1 at 64% (95% CI 23.0%, 42.1%) and 6.8 (95% CI 5.4, 7.4) months, respectively. The DoR was 9.3 (95% CI 5.5, 12.9) months.

The most commonly reported adverse events (AEs) of any grade, were nausea, reported by 83.7% versus 82.0%, diarrhoea in 76.5% versus 82.0%, and vomiting, which was reported by 60.2% and 64.0% of patients in the ASCEND-1 and -2 trials, respectively. Study discontinuation due to an AE was reported for 10 ASCEND-1 and 7 ASCEND-2 patients. ASCEND-1 (NCT01283516); ASCEND-2 (NCT01685060). Felip *et al.* Abstract 141PD.

Practice point and future research opportunities

Brain metastases represent a common site of disease progression in patients with ALK-positive non-small cell lung cancer (NSCLC), including those who have received crozotinib. Ceritinib demonstrated clinically meaningful whole body and intracranial activity with an acceptable tolerability profile crizotinib-pretreated patients with ALK-rearranged NSCLC and baseline brain metastases.

Combination bevacizumab/pemetrexed outperforms sole pemetrexed as maintenance therapy in advanced non-squamous NSCLC: Results of the expanded SAKK19/09 trial

Oliver Gautschi, Luzerner Kantonsspital in Luzern, Switzerland presented findings on behalf of colleagues from the expanded SAKK19/09 phase II trial of bevacizumab plus pemetrexed compared to pemetrexed alone as maintenance therapy. SAKK19/09 initially treated 77 patients with 4 cycles of cisplatin at 75 mg/m^2, pemetrexed at 500 mg/m^2 plus bevacizumab at 7.5 mg/kg every 3 weeks, followed by bevacizumab/pemetrexed maintenance until RECIST progression; the trial was expanded to treat 52 patients with only the same chemotherapy regimen without bevacizumab.

The trial's primary endpoint of progression-free survival (PFS) was met; median PFS was 6.9 months; 95% CI 5.2, 8.4 months with combination bevacizumab and pemetrexed versus 5.6 months; 95% CI 4.3, 6.8 months with sole pemetrexed. The overall response rates (ORR) were 62% with bevacizumab/pemetrexed, 95% CI 51%, 73% versus 44% with pemetrexed; 95% CI 31%, 59%. Combination therapy improved both PFS and ORR over pemetrexed, respectively, HR 0.7; 95% CI 0.5,1.0 (p = 0.04) and odds ratio 2.1; 95% CI 1.0, 4.3 (p = 0.05). Although no significant difference in overall survival (OS) was observed between treatment groups, OS is being further investigated in an ongoing phase III trial.

Adverse events grade ≥ 3 occurred at a slightly higher rate with bevacizumab plus pemetrexed than with pemetrexed but were manageable in both arms.

The investigators performed a preliminary economic analysis and determined that treatment cost was approximately 1.6 times higher with bevacizumab/pemetrexed over pemetrexed at $10,226/month versus $6,251/month, respectively. NCT01116219. Gautschi *et al.* Abstract 143PD.

Practice point and future research opportunities

Maintenance therapy with bevacizumab and pemetrexed increased overall response rates and progression-free survival over sole pemetrexed but not overall survival in patients with advanced non-small cell lung cancer (NSCLC). Findings from the SAKK19/09 trial are in accord with the PARAMOUNT trial, which demonstrated benefit from pemetrexed maintenance therapy in patients with advanced, non-squamous NSCLC and AVAPERL, which demonstrated encouraging results with bevacizumab and pemetrexed compared with sole bevacizumab.

PD-L1 polymorphism may predict clinical outcomes in patients with NSCLC treated with first-line paclitaxel-cisplatin

A team of investigators headed by S. K. Do, Kyungpook National University, Daegu, Republic of Korea conducted this study to investigate whether polymorphisms of genes involved in immune checkpoints can be predictive of clinical outcomes in patients with advanced non-small cell lung cancer (NSCLC) following first-line paclitaxel-cisplatin chemotherapy. This analysis comprised 379 NSCLC patients and evaluated 12 single nucleotide polymorphisms (SNPs) of PD-1, PD-L1, and CTLA-4 genes for an association with the response to chemotherapy and overall survival (OS).

The authors determined that PD-L1 rs2297136T>C and rs4143815C>G SNPs were significantly associated with clinical outcomes following first-line paclitaxel-cisplatin; rs2297136T>C was significantly associated with patients showing a better response to chemotherapy and better OS, and the rs4143815C>G associated only with a significantly better response to chemotherapy. Consistent with the individual genotype analyses, patients having the rs2297136C-rs4143815G haplotype (ht4) carrying variant alleles at both loci showed significantly better chemotherapy response and OS, compared with patients having other combined haplotypes. Patients with at least one ht4 had significantly better chemotherapy response and OS compared to those without ht4. DO *et al.* Abstract 155P.

Practice point and future research opportunities

These study findings suggest that single nucleotide polymorphisms PD-L1 rs2297136T>C and rs4143815C>G may have utility as predictors of clinical outcome following first-line paclitaxel-cisplatin chemotherapy in NSCLC. In particular, patients having at least on ht4 fared better than patients without ht4. Further evaluation is needed to confirm these findings and to understand the role of PD-L1 in the outcome of NSCLC patients following chemotherapy.

METASTASES TO AND FROM THE LUNG

Dosimetric predictor of toxicity in multiple lung tumours treated with stereotactic ablative radiotherapy identified

Hilâl Tekatli, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands and colleagues conducted a multi-centre retrospective study to determine outcomes and dosimetric parametres in patients with multiple lesions treated with stereotactic ablative radiotherapy (SABR). The study comprised patients undergoing SABR within one month for 2 or more synchronous parenchymal lung lesions from 2009 to 2014 recorded in either the VU University Medical Centre or London Health Sciences Centre databases. Patients with prior or subsequent non-SABR thoracic radiotherapy were excluded. A total of 84 patients underwent SABR using Volumetric Modulated Arc Therapy and 187 lesions received a biological equivalent dose $(BED)_{10}$ of ≥100Gy. Of these patients, 97% were treated for 2 to 3 lesions, and 56% had bilateral lesions; 46% of patients overall received treatment for multiple lung metastases, and 54% underwent SABR for multiple primary NSCLC lesions. The patients' median age was 69.4 years,

After a median follow-up of 28 months, median overall survival (OS) was 35 months. The 5-year survival rate was 39%. Toxicities of grade 2 or greater were reported for 20% of patients at 6 or more weeks following the beginning of SABR treatment. Nine patients had radiation pneumonitis (RP), 5 reported chest wall pain, 2 had rib fractures, and one patient reported dyspnoea. One treatment-related death occurred from RP. Non-treatment related deaths included 17 due to progressive disease, and 15 due to other causes.

Most plan optimisations severely constrained the V_{5Gy} of the contralateral lung. On multivariable analysis, total lung minus the planning target volume (PTV) V35Gy of 6.5% or more in 2 Gy/fraction equivalent significantly associated with the occurrence of grade 2 or higher RP (p = 0.007). Tekatli *et al.* Abstract 197PD.

Practice point and future research opportunities

This first report on predictors of toxicity after SABR for multiple lung lesions identifies a possible predictor for SABR toxicity, especially radiation pneumonitis. However, these findings should be further investigated in expanded patient populations, and using other SABR delivery techniques.

Development and validation of a nomogram for predicting overall survival following stereotactic body radiotherapy for pulmonary metastases

Lead author Mathias Guckenberger of the Department for Radiation Oncology, Universitätsspital Zürich in Zürich, Switzerland, cited better recognition and understanding of oligo-metastatic disease for the increased frequency that radical treatment of pulmonary metastases is being practiced. The study generated and tested a nomogram for overall survival (OS) following stereotactic body radiotherapy (SBRT) for pulmonary metastases to improve patient selection. The investigators

used a database comprising 23 institutions (DEGRO Working Group Stereotaxy) wherein 671 patients were treated with SBRT for 964 pulmonary metastases as a training cohort. Cox regression analysis with backward selection of variables (Akaike information criteria) was performed to identify factors included in the model in order to predict OS at two years post SBRT. A nomogram was constructed based upon this model, calibrated, and validated using concordance-index statistics. The nomogram was externally validated using a monocentric database of 92 patients treated with SBRT for pulmonary metastases at the University Hospital Aarhus.

The 2-year OS of the training cohort was 52.5%. The Cox model identified Kanofsky performance index, type of the primary tumour, control of the primary tumour, maximum diameter of the treated metastasis, and the number of metastases as significant prognostic factors for OS (all $p < 0.05$). The calculated concordance-index for the nomogram was 0.711.

Based on the nomogram, the training cohort was divided into 4 groups of increasing risk; 2-year OS rates in the respective groups of 76.1%, 62.6%, 45.8%, and 24.2% were predicted. Kaplan-Meier analysis demonstrated 2-year OS rates of 78.4%, 60.4%, 46.0%, and 30.2%. The nomogram discriminated well between risk groups in the validation cohort: Kaplan-Meier based 2-year OS were 84%, 53%, and 40% for risks groups 1 through 3; however, the fourth risk group had insufficient patient numbers of just 4 patients for analysis. Guckenberger *et al.* Abstract 198PD.

Practice point and future research opportunities

Patient selection for SBRT remains challenging with long-term overall survival demonstrated in less than 25% of patients. This study generated and validated a nomogram for prediction of predicting overall survival two years after patients underwent SBRT for pulmonary metastases. Primary tumour histology emerged as an important factor influencing OS, as did control of the primary tumour, and the number and maximum diameter of metastases. However, further evaluation of the nomogram in larger patients populations is warranted. Future prognostic scores may benefit from incorporation of the genetic variability within the different cancer types.

A five-year retrospective study of skin metastases from lung cancer

Tamara Ćulibrk, Department of Radiology, Institute of Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia and colleagues conducted a retrospective study of 47 patients diagnosed with lung cancer and metastasis to the skin from January 1, 2010 to December 31, 2015 at their institute. Skin metastases are rare, and of 7748 patients diagnosed with lung cancer during this period in this institution, just 47 (0.6%) patients were also diagnosed with skin metastasis. These 47 patients included 37 men and 10 women with a mean age of 60.8 (±8.7) years; the majority (91.5%) of patients were current smokers.

Lung cancer was diagnosed by bronchoscopy in 55.3% of the patients, and in 40.4% of patients the lung cancer diagnosis was made from a skin metastasis sample obtained on average 1.6 months later. A simultaneous diagnosis of lung cancer and skin metastasis was made in 31 (66.0%) patients, whereas the diagnosis of skin metastasis preceded that of lung cancer in 10 (21.3%) patients. Six patients

diagnosed with lung cancer developed skin metastasis up to 12 months later. Skin metastases were singular in 63.8% of patients and the remaining 36.2% of patients had multiple skin metastases. The location of the metastases was primarily the chest, back, and abdomen. Most metastasis were nodular in form, with a mean size of 2.4 (±1.2) cm, and the metastases were painful in 53.2% of the patients

Adenocarcinoma was diagnosed in 29 (61.7%) patients. Tissue samples were available for 22 patients and testing for EGFR mutation showed that all samples had wild type EGFR.

Treatment consisted of chemotherapy for 34 (72.3%) patients and 13 (27.7%) patients received only supportive care. The patients receiving chemotherapy survived for a mean 6.9 (±31) months, whereas patients receiving symptomatic therapy lived for 3.11 (±1.2) months. Ćulibrk *et al.* Abstract 202P.

Practice point and future research opportunities

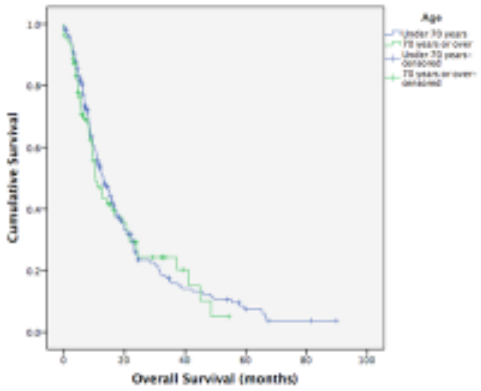
Skin metastases from lung cancer are diagnosed rarely and occur in 0.1% to 12% of patients with lung cancer. Skin metastases from lung cancer are associated with advanced disease and carry a poor prognosis. The diagnosis of skin metastasis was synchronous with the diagnosis of lung cancer in the majority of patients, but the diagnosis of skin metastasis preceded the diagnosis of the primary tumour in approximately a quarter of the patients, with the remaining patients being diagnosed with skin metastases up to a year following the primary diagnosis. Survival was improved by chemotherapy compared with supportive care. All tissue samples tested for EGFR showed wild-type EGFR.

MESOTHELIOMA

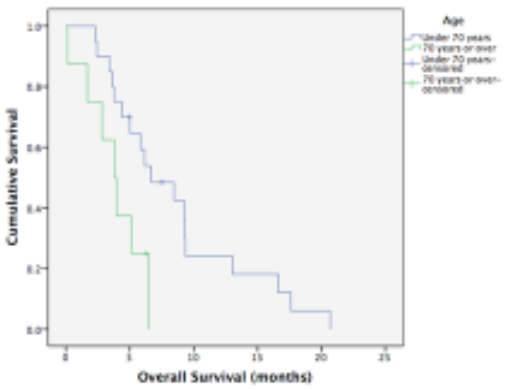
Rigorous preoperative assessment urged for older patients with mesothelioma prior to extended pleurectomy decortication

Lead author Annabel Sharkey, Department of Thoracic Surgery, Glenfield Hospital, Leicester, UK presented findings that supported taking a more selective approach for patients over 70 years when considering extended pleurectomy decortication (EPD). Dr. Sharkey and colleagues reviewed data on patients undergoing EPD that were prospectively collected form from 1999 to 2015 to compare clinical, pathological, outcome and survival data from patients older than 70 years compared with patients younger than 70 years. EPD was performed in all patients with the intent of achieving macroscopic complete resection. Of 282 patients in this overall cohort, 79 (28.0%) patients were 70 years or over at the time of EPD but other demographic and pathological characteristics were balanced between the two groups.

On multivariate analysis, 2 variables emerged as poor prognostic factors for patients overall: Lack of adjuvant therapy, HR 2.088; 95% CI 1.372, 3.176 (p = 0.001) and the presence of pre-operative anaemia, HR 1.976; 95% CI 1.294, 3.017 (p = 0.002). Age did not emerge as a significant prognostic factor of outcome, which was similar between the 2 groups regarding several parametres: In comparison with younger patients, those older than 70 years had a similar length of hospital stay of median 14 days (range: 2 to 93 days) compared with median 12 days (range: 0 to 70 days), in patients younger than 70 years (p = 0.118). Mortality rates were also similar between the groups following EPD; no intergroup difference was observed between in-hospital mortality rates of 3.5% in younger versus 6.5% in elderly patients (p = 0.323), or 90-day mortality of 7.9% versus 10.1% in younger versus older patients, respectively (p = 0.635). Statistically similar overall survival (OS) was observed of 13.0 months compared with 10.5 months in younger and older patients, respectively (p = 0.683).



Overall survival of patients <70 or ≥ 70 years of age



Overall survival of patients with non-epithelioid and node positive tumours <70 or ≥ 70 years of age

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However, disease characteristics and lack of post surgical adjuvant chemotherapy more greatly impacted outcome in the elderly. Among patients with node positive non-epithelioid tumours, the elderly experienced significantly decreased survival of 3.8 months compared with 6.6 months in younger patients (p = 0.024). A significantly greater proportion (16.8%) of elderly patients required intensive care after EPD compared with 5.4% of younger patients (p = 0.004) and atrial fibrillation was seen in 14.4% of younger compared with 24.7% of older patients (p = 0.051).

Fewer patients over 70 years of age received adjuvant chemotherapy post EPD, suggesting that they were not fit enough; 29.6% of elderly patients received adjuvant chemotherapy compared with 45.7% of younger patients (p = 0.040).

Professor Sharkey underscored that malignant pleural mesothelioma occurs frequently in the older population; for examples, the median age at diagnosis in the UK is 72 years. These findings showed that age as an isolated variable was not prognostic of outcome following EPD but other factors, such as the presence of more advanced disease, had a greater negative effect on the outcome of older compared with similar, younger patients. Sharkey *et al.* Abstract 207O.

Practice point and future research opportunities

If a macroscopic complete resection is achievable, extended pleurectomy decortication associates with reduced morbidity and mortality and is preferred over extrapleural pneumonectomy. However, extended pleurectomy decortication may generate worsening of pulmonary function and quality of life (QoL) in patients with minimal symptoms. In symptomatic patients, extended pleurectomy decortication generates a significant and lasting improvement of QoL, whereas pulmonary function is unaffected. Transition from extrapleural pneumonectomy to extended pleurectomy decortication may enable surgeons to offer a surgical option to more patients with performance status 1 and it is characterised by a better survival in the elderly (older than 65 years) compared to younger cohorts.

The age cut-off chosen for this study was different from other publications. It was not stated whether selection of the patients for surgery was based upon an institutional algorithm or a score, or whether a propensity score analysis was done. The routine risk assessment model is not described nor was it stated whether CPET was the standard for preoperative evaluation of these elderly patients. The impact of patient's preference in surgical decision-making was not discussed. The authors noted an increasing late reoperation rate for extended pleurectomy decortication in transition from extrapleural pneumonectomy to extended pleurectomy decortication; it is unclear whether this rate applies to the elderly category and how it affects the subjective and objective outcomes.

Novel vaccine strategy shows promising activity in malignant pleural mesothelioma

Lead author Thierry Jahan of the UCSF Helen Diller Family Comprehensive Cancer

Center in San Francisco, USA explained that CRS-207 is a live, attenuated Listeria monocytogenes bacterium that was altered to decrease toxicity and to activate immunity by directing expression of the tumour-associated antigen mesothelin. Mesothelin is over-expressed in virtually all epithelioid, but not sarcomatoid, cases of malignant pleural mesothelioma (MPM). His team had also noted that CRS-207 worked synergistically with chemotherapy, which led to this study that evaluated the effect of CRS-207 combined with standard pemetrexed and platinum chemotherapy in patients with advanced unresectable MPM.

The study enrolled 37 patients who were given two CRS-207 infusions 2 weeks apart, plus up to six cycles of pemetrexed plus cisplatin 3 weeks apart, followed by two additional CRS-207 infusions 3 weeks apart. All patients were assessed every 8 weeks until disease progression, and eligible patients received maintenance CRS-207 every 8 weeks. As of August 2015, 30 patients had completed the full treatment course and 19 of completing patients had received at least one maintenance treatment with CRS-207.

After median follow-up of 9.4 (range: 0.2 to 28.1) months, data were evaluable for 34 patients that demonstrated greater than 90% disease control. The best overall response was partial response in 20 (59%) patients, and stable disease in 12 (35%) patients. One (6%) patient experienced progressive disease. Tumour shrinkage was confirmed in 85% of patients. Median progression-free survival was 8.5 months.

Combined CRS-207/chemotherapy was well tolerated. There was one (3%) report of severe grade 3 CRS-207 infusion-related adverse event of fever, 2 (6%) cases of chills/rigors, and one (3%) report of hypotension.

Immunohistochemistry analysis was carried out in samples from 3 patients that showed immune activation with marked recruitment and expansion of tumour infiltrating leukocytes following the administration of the therapy. There was also an enhancement of infiltrating CD8+ cells, macrophages, and natural killer cells. NCT01675765. Jahan *et al.* Abstract 208O.

Practice point and future research opportunities

Malignant pleural mesothelioma is a cancer of the lining of the lung that is rare but has a poor prognosis and is difficult to treat; most patients are not candidates for surgical resection. There is a clear unmet need in this specific population wherein the standard of care treatment with pemetrexed and platinum compound chemotherapy shows a 30% response rate but a modest impact on survival. In this study, immunotherapy with CRS-207, a live bacterium, combined with chemotherapy demonstrated disease control greater than 90% and a 59% response rate in patients with malignant pleural mesothelioma.

These preliminary results are encouraging, and suggest superior clinical activity when the vaccine is added to standard chemotherapy. These findings support assessing the impact of CRS-207 in a randomised trial, which is currently in the planning stages and should be underway within this calendar year.

SMO mutation associates with shorter overall survival in malignant pleural mesothelioma

Diego Signorelli, Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori in Milano, Italy, and colleagues conducted a study to identify a gene profile that could separate patients with malignant pleural mesothelioma (MPM) demonstrating short-term survival from the approximately 10 to 15% of MPM patients who are long-term survivors. The investigators used DNA from retrospectively collected formalin-fixed paraffin-embedded tissue samples obtained from 57 patients with MPM and the PGM Ion Torrent platform to analyse a panel of 21 genes: CDKN2, NF2, GSTM1, NAT2, BAP1, TERT, P53, PTCH1, SMO, LATS2, KEAP1, PI3K, KRAS, NRAS, STK11, WT1, FBXW7, CTNNB1, KIT, KDR, and REV3. Expression of SMO and GLI proteins, involved in the Hedgehog pathway, was also evaluated by immunohistochemistry (IHC) in 11 samples. The hazard risk of death was calculated with the Cox Model. The cut-off defining short versus long survival was 36 months.

The main clinical prognostic factors of age, sex, histotype, stage, and treatment were equally distributed between the two groups. The BAP-1 gene was mutated in 24.5% of samples, NF-2 in 17.5%, p53 in 14%, SMO in 8.8%, PTCH1 in 8.8%, KEAP1 in 7%, and TERT was mutated in 5.3% of samples. In the overall population, 31.6% of the patients were wild-type for the gene panel.

The short survival cohort contained 33 patients that demonstrated median overall survival (OS) of 13 months compared to OS of 47 months for the 24 patients in the long survival cohort. No major differences in gene profile were observed between short and long survivors. However, SMO was mutated only in patients in the short survival cohort where 16% of patients showed this mutation. SMO mutation emerged as a strong negative prognostic factor for the entire population, HR 8.01; 95% CI 2.79, 22.98 ($p < 0.001$). In the short survival cohort, SMO mutation again was a statistically significant negative factor, HR 3.67; 95% CI 1.28, 10.48 ($p = 0.015$). SMO mutated patients demonstrated median OS of just 7 months.

IHC revealed no differences in SMO and GLI protein expression in 5 samples showing SMO gene mutation and 6 samples that were wild type for all sequenced genes. Signorelli *et al.* Abstract 209P.

Practice point and future research opportunities

Malignant pleural mesothelioma is a rare and aggressive cancer with limited therapeutic options, and median overall survival that rarely exceeds 18 months. However, a better prognosis with longer overall survival has been reported in about 10% to 15% of patients. In this analysis, a mutation in the SMO gene seems to identify a subset of mesothelioma patients with a poorer prognosis. SMO plays a role in the Hedgehog pathway and may be a target for specific inhibitors, warranting the ongoing preclinical and clinical studies investigating SMO and its effectors in mesothelioma.

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ELCC European Lung Cancer Conference, 05-08 May 2017, Geneva, Switzerland.

Affiliation and Disclosure

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Disclosure

No conflicts of interest to declare.

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