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Summary

Held once again in Geneva, Switzerland from April 15 to 18, 2015, the European Lung Cancer Conference (ELCC) brought together leading investigators and experts in the field of lung cancer and other thoracic tumours from around the world. Organised by the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC), ELCC 2015 provided opportunities for attendees to meet top experts in the lung cancer field, share information and form new collaborations. Participants left the Conference with a quality overview of current areas of research, inspiration and renewed focus in their endeavour to provide the best medical care available for patients with lung cancer.

The scope of this report is to present the scientific highlights of the ELCC 2015 Conference.

Introduction

This year's meeting was attended by 1,461 delegates and, taken together with invited speakers, industry exhibitors, and press, overall attendance topped 1676, a hearty 20.1% increase over last year. Delegates came from 70 countries around the globe, with the UK, the USA, Switzerland, Germany, Italy, Austria and China represented by the largest number of delegates. Some travel was facilitated by travel grants, which were awarded to 20 delegates.

Attendees could choose from a broad range of educational workshops plus controversy, proffered paper, poster and Young Oncologist sessions, where experts presented the latest results from clinical trials, novel immunotherapies, biomarker research, surgical techniques and radiotherapy.

The plenary sessions covered diverse topics, as always, that included surgical and radiological strategies for advanced disease, the growing field of biomarkers and the work underway to find more, the ever-expanding role of immunotherapy, plus new approaches in the treatment of mesothelioma. Up-to-date overviews and discussions of the most promising new targets and novel targeted agents in on-going or recently completed clinical trials were presented. Newly developed and/or approved immunological agents and a wide range of promising targeted agents were discussed by experts in their respective fields. Also presented were many papers on new approaches to evaluating tumour response and novel applications of genetic analysis techniques, all aiming to provide optimal clinical treatment for every patients.

This year also marked the joint announcement of ESMO and the IASLC that the ELCC will become an annual meeting as of 2015. ELCC will continue to promote cooperation among the societies representing thoracic oncology specialists (European Society for Radiotherapy & Oncology, European Society of Thoracic Surgeons and European Thoracic OncologyPlatform) and provide a multidisciplinary forum to optimise patient care and the practice of lung cancer throughout the world.

ESMO–IASLC BEST ABSTRACTS SESSION

The ESMO–IASLC Best Abstracts session, held on the afternoon of 17 April, was chaired by Dominique Grunenwald, Hospital Tenon, University of Paris, France and Johan Vansteenkiste, University Hospitals, Leuven, Belgium. Following is a synopsis of presentations from the session outlining state of the art methods of mutation detection and prospective biomarkers of response. The session was rounded out with comments by invited discussants Egbert Smit, Netherlands Cancer Institute and Vrije Universiteit VU Medical Centre, The Netherlands and Tony Mok, The Chinese University of Hong Kong, China.

Circulating tumour DNA in blood provides an option for EGFR testing in patients without accessible tumour tissue

Martin Reck, Department of Thoracic Oncology at Lung Clinic Grosshansdorf, Germany, began the session with findings from ASSESS, a study showing that DNA found in the bloodstream of lung cancer patients can provide useful mutation information for optimised treatment in the absence of available tumour tissue. Previous studies suggested that DNA from the tumour circulating in the bloodstream of patients may provide similar information regarding the mutational status of the tumour as an actual tumour biopsy, leading an international team of investigators to conduct ASSESS, which aimed to compare detection of epidermal growth factor receptor (EGFR) mutations by blood testing to the ‘gold-standard’ of testing the tumour.

Matched tissue and blood samples were obtained from 1162 patients, 881 patients from Europe and 281 from Japan. Several testing moieties were used for tissue and plasma in Europe, whereas Cycleave and Qiagen Therascreen® EGFR Pyro Kit were used for both in Japan. The median turn-around time was 11 days in Europe compared to 8 days in Japan, with an average test success rate of 98.3% versus 99.6%, respectively. Comparison of the overall outcomes of EGFR testing showed an 89.1% concordance rate between the blood and tissue tests (95% CI 87.1, 90.8). The positive predictive value (PPV) was 77.7% (95% CI 68.8, 85.0) and the negative predictive value (NPV) was 90.3% (95% CI 88.3, 92.0). Comparison of results obtained by using the same method in 254 samples, as opposed to using different methods in 908 samples, yielded concordance of 87% versus 89.6%, respectively. PPV was improved to 92.6% using the same method versus 62% with different methods and the NPV was 86.3% versus 91.4%, respectively, when same and different methods were used. Plasma testing identified about half of the patients with EGFR mutations identified by tissue testing, yielding sensitivity of 46%.

Prof. Reck pointed out that all testing in this study was done in local laboratories that are used for daily clinical routine rather than special centralised laboratories; therefore, the results represent the clinical reality. (Reck *et al.* Abstract 350)

Practice point and future research opportunities

The results of this study validate that the presence of EGFR mutations in circulating DNA from plasma or serum can be detected in around half of the patients. Cell-free DNA detected in the bloodstream of cancer patients represents an excellent tool to examine the genetic status of the tumour when insufficient tumour DNA is available at diagnosis. A good PPV can be obtained, bearing in mind that the testing methods used affect the results. More studies are needed to establish the value of testing circulating tumour DNA in the blood during therapy, but it may mean that patients without accessible tumour tissue may still be offered adequate targeted treatment, based on plasma testing for EGFR mutation.

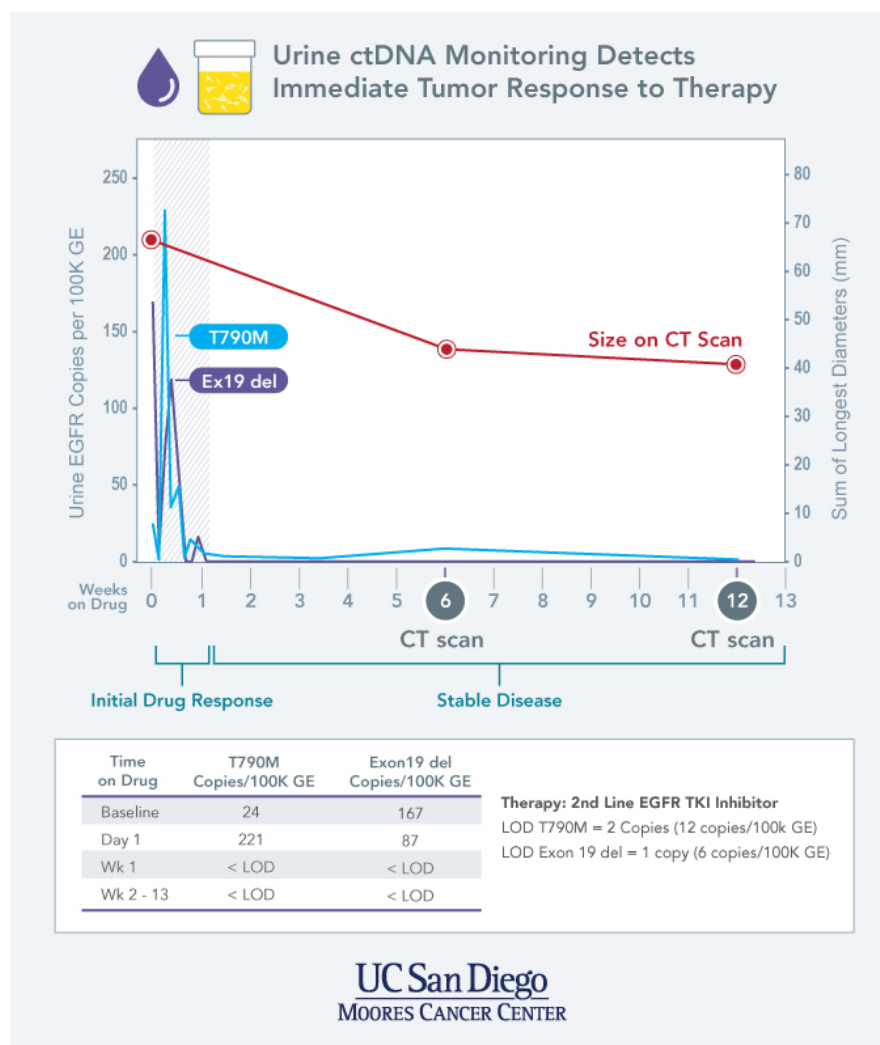
EGFR T790M resistance mutations in non-small cell lung cancer assessed by 'liquid biopsy'

Lead investigator Hatim Husain, Moores Cancer Center, University of California, San Diego, USA, discussed how response to therapy and disease progression in patients with metastatic non-small cell lung cancer (NSCLC) may be monitored using an assay of circulating tumour DNA (ctDNA), isolated from the urine of patients. Resistance mutations that decrease the efficacy of tyrosine kinase inhibitors (TKIs) are often acquired by tumours, necessitating continued genetic assessment over the course of the disease; *T790M* mutation is the primary mechanism of resistance to first generation of anti-EGFR inhibitors and is implicated in 60% of cases. Results were presented demonstrating that *EGFR T790M* resistance mutation could be detected in ctDNA present in patients' urine, which is used for this assay because ctDNA in the blood is excreted in urine where the yield is 10 times greater due to the larger volumes collected. The study presented at ELCC had 3 specific aims: to determine the concordance between this assay compared with tissue biopsy for detection of *T790M*, the second aim tested the hypothesis that *T790M* could be detected earlier on than radiographic progression and the third study aim tested whether the pharmacodynamics of ctDNA within the first week could predict the radiographic response to second-line TKIs.

Evaluation was done of ctDNA in urine samples from 22 patients undergoing treatment with anti-EGFR agents for metastatic NSCLC. ctDNA was extracted by a method preferentially isolating short, fragmented ctDNA and quantified using the droplet digital polymerase chain reaction (ddPCR); the yield average was 0.4 µg total amplifiable ctDNA per sample (range: 0.04 to 2.4 µg). It was further determined that the assay could detect *EGFR T790M* with a lower limit of detection of two copies within a background of 60 ng of wild-type DNA, yielding an analytical sensitivity of 0.01%. *T790M* mutation was detected in 10 out of 10 patients with tissue-confirmed *T790M* making the sensitivity 100%.

EGFR *T790M* mutation was detected in 15 of 22 (68%) of patients receiving anti-EGFR treatment until progression. Urine EGFR *T790M* mutation was detected in 10 out of 10 tissue-positive patients, giving 100% concordance. Urine ctDNA testing identified 5 additional patients who may be eligible for treatment with anti-*T790M* drugs, 3 with *T790M* negative tissue and 2

with T790M unknown by tissue. Seven patient samples were T790M negative in the urine biopsy and unknown by tissue.



Caption: Drug induced apoptosis is indicated by peaks of T790M/Exon 19 deletion mutations in urine ctDNA immediately following therapy, while the subsequent decrease in urine ctDNA mutations is associated with a decrease in tumor burden. © Hatim Husain

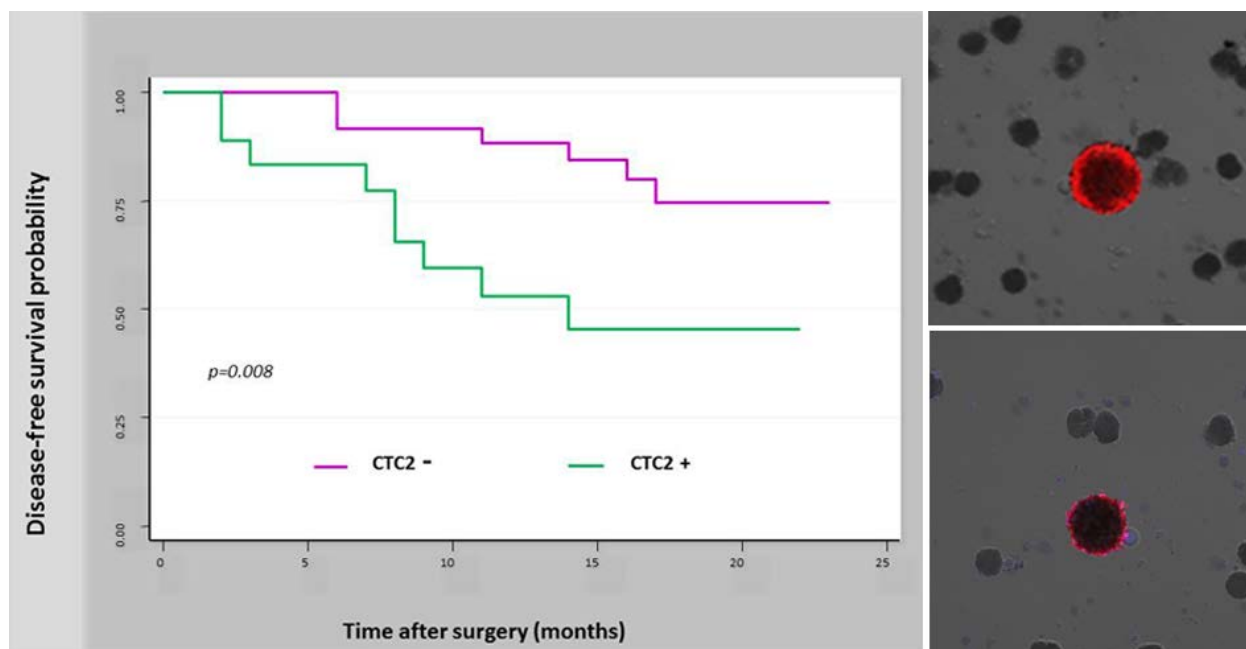
The investigators showed that EGFR T790M mutation can be detected in urinary ctDNA up to 3 months before radiographic progression on first-line anti-EGFR TKI. When T790M positive patients were treated with third generation anti-EGFR TKIs, a decrease in ctDNA T790M load was observed as early as 4 hours after therapy on first day of treatment. The initial decrease in T790M levels was followed by a spike in T790M later on in the first week of therapy. Studies to understand whether there is a correlation between the size of spikes, tumour burden and/or variation in response are ongoing. (Husain *et al.* Abstract 36O) The study was funded by Trovogene, Inc.

Practice point and future research opportunities

An alternative to sequential, invasive tumour biopsies, which are often difficult to obtain, using an assay of urine ctDNA isolated by an ultra-sensitive next generation sequencing (NGS) mutation enrichment method may provide the accurate clinical status of patients. EGFR T790M mutation load was detected in urinary ctDNA that was confirmed by tumour tissue biopsy, potentially providing measurement of response to anti-EGFR therapy. In addition, detection of EGFR T790M was possible with this assay months before it could be detected by radiology. Further confirmation of these findings in a large clinical trial is warranted.

Detection of circulating tumour cells following resection for NSCLC may indicate elevated risk of early recurrence

Clara Bayarri-Lara, Department of Thoracic Surgery, Hospital Universitario Virgen de las Nieves, Granada, Spain presented results on behalf of colleagues demonstrating that circulating tumour cells (CTCs) can be isolated from some patients' blood after radical resection for NSCLC and their presence may be prognostic of relapse. This prospective study enrolled 56 previously untreated patients who underwent radical surgery for NSCLC. CTCs were isolated using both an immunomagnetic technique and by size from blood samples taken prior to and one month after resection. Patients were identified as CTC-positive if at least one CTC per sample was isolated; 29 (51.8%, median number of CTCs = 3) patients were CTC-positive prior to surgery and 18 (32.1%, median number of CTCs = 2) patients were CTC-positive one month following resection ($p = 0.035$). CTC detection was determined to be significantly lower following pneumonectomy compared to other surgeries ($p = 0.034$). The CTC count in the post-surgical samples showed an association with the max SUV of PET scan ($p = 0.046$) but no other analysed parameter. CTC EGFR expression was 89.7% and 38.9% in samples taken before and after surgery, respectively.



Caption: Detection of circulating tumour cells one month after surgery (CTC2 +) was significantly correlated with a shorter disease-free survival in patients undergoing radical resection for non-small-cell lung cancer. © Clara Bayarri-Lara

Disease recurrence was seen in 16 (28.6%) patients during follow-up of median 16 months; recurrence significantly associated with CTC presence after surgery ($p = 0.018$). Patients with a CTC-positive post-surgical sample also experienced shorter disease free survival (DFS) at 1-year of 51% compared to 87.7% of CTC-negative post-surgical patients (log rank test $p = 0.008$). Disease recurrence significantly associated with the detection of CTCs in post-surgical blood samples ($p = 0.018$). Multivariate analysis identified the presence of CTCs following surgery ($p = 0.010$) and node status ($p = 0.043$) as independent prognostic factors for DFS. (Bayarri-Lara, *et al.* Abstract LBA1)

Practice point and future research opportunities

CTCs can be detected in blood samples of some patients following radical resection for NSCLC and may indicate an increased risk for early disease recurrence; the presence of CTCs and node status are independently prognostic of disease-free survival; however, more robust isolation methods are needed before this technology can be routinely applied in clinical practice.

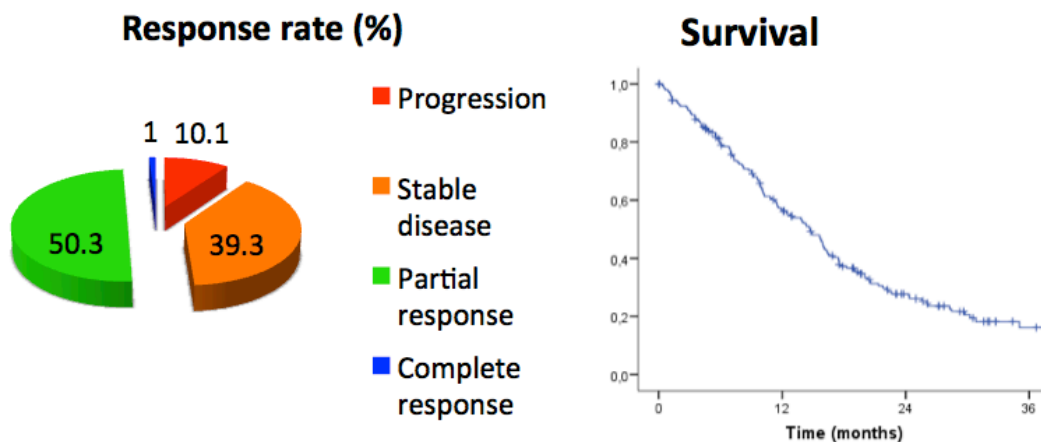
TRANSLATIONAL RESEARCH

Identification of potential predictive markers for bevacizumab activity in patients with advanced non-squamous non-small cell lung cancer: Final results of ANGIOMET Spanish Lung Cancer Group Trial of bevacizumab added to carboplatin and paclitaxel

Bartomeu Massuti Sureda, Department of Medical Oncology, Hospital General Universitario de Alicante, Alicante, Spain presented final efficacy results and an identification of predictive biomarkers from the ANGIOMET trial on behalf of the Spanish Lung Cancer Group. ANGIOMET was a prospective clinical trial of first line bevacizumab plus carboplatin and paclitaxel in 202 patients with advanced stage IIIB/IV non-squamous NSCLC. Patients' median age was 61 years (range: 37 to 80 years), 67.2% of patients were male, all were Caucasian, 97.8% had stage IV disease, which was mostly (88.2%) adenocarcinoma, and 15.8% of patients were never-smokers. The per protocol population comprised 199 patients who received a median five cycles of carboplatin/paclitaxel plus bevacizumab.

ANGIOMET: a Spanish Lung Cancer Group Trial

202 p with non-squamous advanced NSCLC treated with Carboplatin-Paclitaxel-Bevacizumab



Median survival: 14,7 m (12,3-17,1).; 6-m surv: 79,5%
1-y surv: 56,8% ; 2-y surv: 27,8%

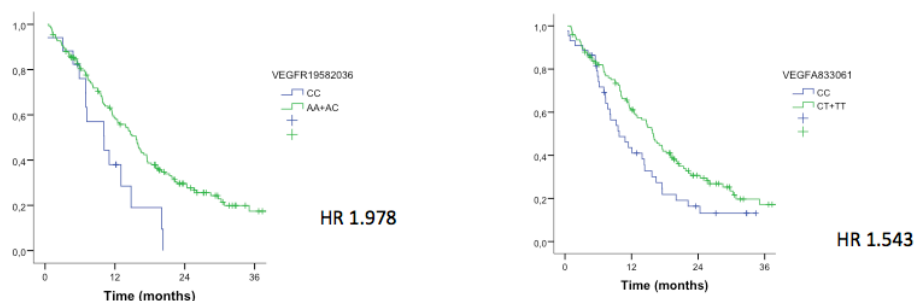
Caption: Response rate and survival in the ANGIOMET study. © Bartomeu Massuti Sureda

The trial's primary end-point, PFS and secondary endpoints, overall survival (OS) and response rate (RR) were met. Patients achieved median PFS of 6.91 (range: 6.16 to 7.65) months and OS of median 14.57 months (range: 11.83 to 17.31 months). In the intent to treat population of 171 patients, complete response was achieved by 1% of patients, 49% of patients showed partial response, 36% of patients had stable disease and progressive disease occurred in 10.6% of patients. The response in 4% of patients was not evaluated.

The ancillary study focused on molecules in the VEGF pathway where several ligands and receptors modulate tumour angiogenesis and therapeutic efficacy. DNA was obtained from blood samples taken prior to, and after treatment and the PCR assay was used to genotype SNPs of angiogenic genes. Plasma levels of VEGFA and VEGFR2 were also determined by ELISA.

SNPs as predictive factors

SNPs could modify levels of angiogenic factors and might be correlated with outcomes when Bevacizumab is used
10 SNPs analyzed and correlation with PFS



SNPs VEGFR1 rs9582036 (CC), VEGFA rs833061 (CC), correlates with poor outcomes and SNP VEGFR2 rs 2071559 (AA) show a trend to better outcomes
Lower levels (<median) of circulating VEGF (basal) are associated with significant longer PFS ($p=0.04$) and a trend for OS ($p=0.10$).
SNPs modifying levels of angiogenic factors could be useful as biomarkers for NSCLC patients receiving antiangiogenic

Caption: Ten SNPs analysed in the ANGIOMET study and their correlation with progression-free survival. © Bartomeu Massuti Sureda

Statistical analysis revealed that shorter PFS ($p = 0.01$) and OS ($p = 0.01$) associated with VEGFR1 SNP rs9582036 (CC) and VEGFA SNP rs3025039 (CC) associated with poorer OS, when compared to other genotypes ($p = 0.009$). Overall, lower VEGF levels were prognostic of better outcome; a significant association with longer PFS ($p = 0.04$) and a trend toward improved OS ($p = 0.10$) was observed in patients with levels of circulating VEGF that were lower than those recorded at baseline. (Massuti Sureda *et al.* Abstract 37PD)

Practice point and future research opportunities

The search for reliable biomarkers predicting the efficacy of anti-angiogenic therapies remains an open issue. The investigators found no significant association between response rates and either the SNPs analysed or the levels of VEGF and VEGFR2 in patient blood samples. However, patients having lower VEGF levels in their baseline blood samples experienced improved survival outcomes. Furthermore, it was determined that the presence of certain VEGFR1 and VEGFA SNPs in the blood of patients with advanced non-squamous NSCLC associated with decreased efficacy of the bevacizumab, carboplatin and paclitaxel regimen that was demonstrated by shorter PFS and OS.

Association between miR31-3p expression and survival in patients with advanced lepidic adenocarcinoma treated with EGFR TKI: Results from the IFCT 0401 and 0504 trials

Raphaële Thiebaut, IntegraGen, Evry, France, presented findings from an analysis of the expression of the micro-RNA, miR31-3p, in patients with advanced lepidic adenocarcinoma treated with an EGFR TKI. It is thought that miR31-3p might be involved in EGFR pathway and an association has been reported with PFS in patients with RAS wild-type metastatic colorectal cancer receiving anti-EGFR agents.

RTQPCR was used to measure the miR31-3p expression levels in FFPE primary tumour samples from 48 patients with advanced lepidic adenocarcinoma participating in two randomised phase II trials. In all, 22 patients had received first-line gefitinib and 26 had received first-line erlotinib or paclitaxel plus carboplatin; the studies allowed treatment cross-over after progression or toxicity. The effect of miR31-3p expression level on OS, PFS and disease control rate (DCR) was tested using a Cox proportional hazards model; a merged data-set was built by pooling patients treated in first-line by EGFR TKI (gefitinib, n=22; erlotinib, n=10) to enlarge the sample size. Histologic subtype was taken into account to compare effects of miR31-3p in the mucinous versus non-mucinous subtypes. A p value <0.1 was considered as significant.

The distribution of miR31-3p expression was comparable in both trials. Patients with the non-mucinous tumour subtype showed significantly lower miR31-3p expression than patients with mucinous tumours (p = 0.004). A significant effect of miR31-3p expression was observed for OS in patients with non-mucinous tumours; the OS HR was 1.49 (p = 0.08). Using the merged data set, a strong correlation between the level of mucin expression in tumour cells assessed by periodic acid shift stain and miR31-3p expression was observed; Spearman correlation: 0.73 (p = 0.0002). Expression of miR31-3p was significantly predictive of DCR; OR 1.49 (p = 0.03). (Thiebaut *et al.* Abstract 43P)

Practice point and future research opportunities

Expression of miR31-3p is lower in non-mucinous tumours than in mucinous tumours and miR31-3p expression associates significantly with OS in patients with lepidic adenocarcinoma receiving EGFR TKI. miR31-3p expression also associated with disease control rate in a

merged dataset. Taken together, these findings suggest that miR31-3p could be marker of clinical benefit with TKI treatment of patients with lepidic adenocarcinoma.

Upregulated miRNA 21 plus KRAS mutation associates with poorer prognosis in patients with resectable non-small cell lung cancer

Sandra Gallach and colleagues investigated whether an association exists between deregulated miRNAs identified in samples taken from resectable NSCLC tumours and the KRAS mutational status. Nucleic acids were isolated from 186 fresh-frozen tumour and normal lung specimens. KRAS mutations were detected by quantitated PCR and RTQPCR, microRNA probes (specific TaqMan microRNA assay kit), were used to determine the expression levels of 22 NSCLC deregulated miRNAs, in paired tumour and normal tissue samples. The statistical significance was defined as $p < 0.05$.

Patients had a median age of 64 years (range: 26 to 82), were 87.6% male, and 66.7 % were ECOG PS 0. Adenocarcinoma was confirmed in 40.9% of patients and mutated KRAS was identified in 11.8 % of patients (12Asp n=7; 12Cys n=7; 12Val n=7 and 12Ser n=1). Shorter PFS and OS were reported for patients with mutated KRAS ($p = 0.017$ and $p = 0.027$, respectively). KRAS mutations significantly associated with miR-21 expression ($p = 0.028$). The investigators found that patients with KRAS mutations and higher levels of miR-21 experienced poorer PFS and OS ($p = 0.002$ and $p = 0.008$, respectively). Prof. Gallach noted that miR-21 expression is upregulated by EGFR/RAS oncogenic signalling, which is in agreement with tumour promoting and anti-apoptotic functions. (Gallach *et al.* 44P)

Practice point and future research opportunities

Upregulation of miR-21 in NSCLC seems to be implicated in the KRAS oncogenic pathway and could serve as a marker to detect patients with early-stage NSCLC at high risk of relapse.

Enumeration and molecular characterisation of circulating tumour cells in lung cancer patients using the GILUPI CellCollectorTM

Lead investigator Nicole Scheumann, Clinical Research, GILUPI GmbH, Potsdam, Germany presented findings from an analysis of a liquid biopsy that relies upon isolating circulating tumour cells (CTCs) from the blood of lung cancer patients. The use of CTCs is currently limited since they are isolated in vitro from small volumes of patient blood samples. This study used the GILUPI CellCollectorTM to isolate CTCs in vivo. The investigators assessed CTC counts in 50 patients with lung cancer prior to the initiation of chemotherapy and 12 weeks afterwards.

This study screened 48 patients with NSCLC and two with squamous cell lung cancer for CTCs by two subsequent device applications at the two time points, yielding 185 applications. Blood samples were also analysed with the CellSearch[®] system. CTCs were isolated from 78% of the patients using the GILUPI CellCollectorTM prior to initiation of treatment. At both time points, a greater quantity of CTCs could be isolated with the GILUPI CellCollectorTM from 58% of patients compared to 28% of patients using CellSearch[®].

The authors found that the GILUPI CellCollector™ for CTC quantification before and after therapy initiation provided information on prognosis, treatment efficacy and molecular tumour evolution. KRAS and EGFR mutations detected in the primary tumour could be detected in CTCs using this method. The CTC count change before and after therapy was associated with clinical response. (Scheumann *et al.* Abstract 50P)

Practice point and future research opportunities

The GILUPI CellCollector™ is useful for overcoming the limitations imposed by limited blood volume, thereby improving CTCs isolation and allows for the enumeration and molecular analysis of CTCs, which provides information on patient response to treatment.

PATHOLOGY/MOLECULAR BIOLOGY

“Real-world” EGFR mutation frequency results from a large population of chemotherapy naive patients with advanced NSCLC: Final results from the IGNITE study

Results from IGNITE, a large multinational, diagnostic, non-comparative, interventional study conducted by Han *et al.*, Shanghai Chest Hospital, Shanghai, China were presented. IGNITE included 3382 patients with advanced NSCLC of both adenocarcinoma and non-adenocarcinoma histology recruited in 90 centres in Russia and the Asian Pacific. Patients were chemotherapy naive, and had local and/or metastatic advanced NSCLC that was either newly diagnosed or represented recurrent disease after resection. All patients were evaluated as ineligible for curative treatment. Tissue and/or cytology were evaluable in 2291 Asian and 924 Russian patients and plasma was evaluable in 1753 Asian and 941 Russian patients, respectively.

Analysis revealed that EGFR mutation frequency, the primary endpoint, varied by country, sample type, and histology. In the Asian patient population, the EGFR mutation frequency by tissue/cytology was 49% in adenocarcinoma, 14% in non-adenocarcinoma and 10% in squamous cell carcinoma, whereas in the Russian population the EGFR mutation frequency was 18% in adenocarcinoma, 4% in non-adenocarcinoma, and 4% in squamous cell carcinoma. The EGFR mutation frequency was lower in plasma with an overall frequency of 22% in adenocarcinoma and 7% in non-adenocarcinoma samples.

The most frequently observed mutation overall was exon 19 deletion only (49% China, 59% Russia), followed by L858R only (42% China, 25% Russia), exon 20 insertions only (2% China, 0% Russia), L861Q only, and G719X (both $\leq 1\%$ overall). Mutation status concordance could be determined in 2581 matched samples. EGFR mutation status concordance data for tumour versus plasma showed that sensitivity (50% vs. 30%) and positive predictive value (93% vs. 39%) were higher in Asia Pacific versus Russia, respectively.

EGFR mutation status was the largest driver of treatment choice in patients with mutation-positive (50%/47% in Asia Pacific/Russia) and mutation-negative (38%/43% in Asia Pacific/Russia) NSCLC. Following EGFR mutation testing, the most common first-line treatment overall for patients with EGFR mutation-positive NSCLC was gefitinib (36%), and cisplatin for patients with EGFR mutation-negative NSCLC (41%); however, this pattern differed between Asia Pacific and Russia. Use of TKIs in patients with EGFR mutation-positive NSCLC varied widely within AsiaPacific, ranging from 92% in Taiwan to 0% in Thailand.

Study population



Cohort attrition, n (%)			
Cohort attrition	Asia Pacific	Russia	Overall
Initially enrolled	2410 (100)	972 (100)	3382 (100)
-no data on tumour sample*	119	48	167
Data available on tumour sample	2291 (95.1)	924 (95.1)	3215 (95.1)
-no data on plasma sample**	657 (27.3)	31 (3.2)	688
Data available on plasma sample	1753 (72.7)	941 (96.8)	2694 (79.7)
Data available on plasma and tumour samples	1687 (70.0)	894 (92.0)	2581 (76.3)

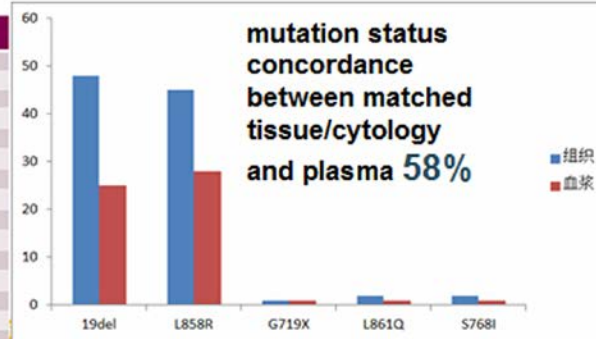
*Insufficient material 54%, Missing 9.2%, Other 4.2%

Source: Table 14.1.1.4.1

**Plasma samples collected only from China (97.5%), Taiwan (100%), S-Korea (96.4%), and Russia (96.8%)

Mutation Frequency % (by tumour)

	Location	Total (%)
Overall EGFR Mutation Positive % (n=1051)	Asia Pac	941 (41%)
	Russia	110 (11%)
SUBTYPE (% of overall positive)		
Exon 19 Del only	Asia Pac	451 (48)
	Russia	63 (57)
L858R only	Asia Pac	409 (44)
	Russia	26 (24)
Exon 20 insertions	Asia Pac	21 (2.2)
	Russia	0 (0)
G719X only	Asia Pac	11 (1.2)
	Russia	0 (0)
L861Q only	Asia Pac	12 (1.3)
	Russia	2 (1.8)
Other rare mutations/double mutations	Asia Pac	37 (6.2)
	Russia	19 (17)



Caption: Determining the prevalence of EGFR mutations in Asian and Russian patients with advanced non-small-cell lung cancer (NSCLC) of adenocarcinoma (ADC) and non-ADC histology: IGNITE study. © Baohui Han

Adenocarcinoma and never-smoker status significantly associated with the mutation frequency in the overall population (both, tissue/cytology and plasma status, $p < 0.0001$). In the Asian versus the Russian cohort (both, $p < 0.0001$), greater number of metastatic organs (tissue/cytology $p = 0.0909$ and plasma $p < 0.0001$), female gender (tissue/cytology only $p = 0.0075$) and age 65 years or greater (plasma only; $p = 0.0009$) significantly associated with EGFR mutation frequency. Immunohistochemistry analyses showed that 10% of TTF-1-negative patient samples were EGFR mutation-positive. Similarly, 44% of TTF-1-positive patient samples were EGFR mutation-positive. (Han *et al.* Abstract 96O) The IGNITE study sponsor was AstraZeneca.

Practice point and future research opportunities

These data from chemotherapy naive patients with advanced NSCLC reveal a higher EGFR mutation frequency in patients with adenocarcinoma versus non-adenocarcinoma histology; however, mutations were seen at a frequency in the non-adenocarcinoma population that supports mutation testing for all patients.

Little is still known about the worldwide epidemiology of EGFR mutations in lung cancer patients. Until now, several national groups have investigated the prevalence of EGFR mutations in large patient subsets. In general, EGFR mutation rate in Asian patients was considerably higher than that in non-Asians. This study looked at the prevalence of EGFR

mutations in Asia and Russia. The results of nearly 50% of EGFR mutations in patients with lung adenocarcinoma in Asia and about 20% EGFR mutated adenocarcinoma in Russia points to specific selection factors, making these data probably not representative of the whole population in Asia and Russia. Data from Russia include more stage IIIA and IIIB patients that represent different patient subsets. Moving EGFR TKI therapy into patient groups with early and locally advanced NSCLC may be more difficult than initially thought; just a bit more than one-third of the patients received EGFR TKI in the first-line setting. These data seem realistic for the everyday practice setting. With broader testing frequencies for EGFR mutations, epidemiological and prevalence data for EGFR mutations should become more precise.

Testing for EGFR mutations can be performed reliably on ultrasound guided supraclavicular lymph node fine needle aspirates

During a poster session, Amir Awwad, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK pointed out that supraclavicular and cervical lymphadenopathy is seen in approximately 15% to 30% of patients with lung cancer and that ultrasound guided fine needle aspiration (FNA) cytology serves as an effective diagnostic tool in small size lymph nodes and impalpable positron emission tomography (PET) detected nodes. However, few data exist on whether this technique also can detect EGFR mutation, leading his team to evaluate the utility of ultrasound guided FNA of supraclavicular and cervical lymphadenopathy with regard to adequacy of samples for detection of EGFR mutations.

Prof. Awwad and colleagues did a retrospective data analysis using the electronic records of 306 patients with suspected lung cancer that had been referred for ultrasound guided FNA of supraclavicular and cervical lymphadenopathy over a four-year period. Of these, 228 patients underwent the procedure and a cytological diagnosis was established in 171 (75%) patients for treatment decisions without further investigations.

Further investigative tests that included core lymph node biopsy, bronchial washings and lung biopsy were done in 57 patients; the diagnosis made by ultrasound guided FNA was re-confirmed in 45 (75%) patients. Positive cytology could be performed in lymph nodes ranging from 3 to 45 mm and the average lymph node size was 12.9 mm. EGFR testing was done in 34 of the 57 patients with adenocarcinoma. Four samples were positive for EGFR mutation, 25 were negative and 5 samples were insufficient for EGFR mutation analysis. The investigators compared ultrasound guided FNA by statistical methods to a composite of all further tests used to identify EGFR mutations and found that ultrasound guided FNA had sensitivity of 76.9% (95% CI 63.2%, 87.5%) and specificity of 100% (95% CI 47.9%, 100%). The positive predictive values of ultrasound guided FNA was 100% in comparison to all further tests, core lymph node biopsy, bronchial washings and lung biopsy. The negative predictive value of ultrasound guided FNA was 29.4%, 20%, 42.9% and 25% compared to all further tests, core lymph node biopsy, bronchial washings and lung biopsy, respectively. The negative likelihood ratio was 0.23, 0.18, 0.3 and 0.4, for ultrasound guided FNA compared to all further tests, core lymph node biopsy, bronchial washings and lung biopsy. The positive likelihood ratio was not available for all

parameters. Patients reported no complication related to any of the procedures performed. (Awwad *et al.* Abstract 5P)

Practice point and future research opportunities

It may not be necessary to obtain additional samples by alternative methods such as bronchial washings and lung or core lymph node biopsy for determination of EGFR mutation status when ultrasound guided FNA has already been taken from patients with supraclavicular and cervical lymphadenopathy. In most patients, ultrasound guided FNA provided reliable EGFR mutation status that was highly sensitive and specific. Furthermore, ultrasound guided FNA gave better positive predictive value information on EGFR mutation in comparison to the other techniques used in this study.

EGFR mutations in patients with non-small cell lung cancer in South Africa

Szewai Chan of the Division of Medical Oncology, University of Witwatersrand, Faculty of Health Sciences, Johannesburg, South Africa, pointed out that currently no data on EGFR mutations in NSCLC had been recorded for the South African population. They conducted this retrospective review to identify factors associated with EGFR mutations, and aimed to determine the estimated rate in South African patients with NSCLC. Data were analysed from patients diagnosed with NSCLC at a South African oncology practices who also had centralised EGFR mutational analysis performed from 1 September 2009 to 30 June 2012. The median patient age was 63 (range: 27 to 85) years and mutation testing was done more often (56%) in women.

Of 170 NSCLC samples that were evaluable for EGFR mutational analysis, 37 (22%) were mutation positive. Twenty-two (60%) samples contained exon 19 deletions, 11 (30%) had L858R mutations, 2 had G719X mutations, one had S768I mutation and one histology sample showed an exon 20 insertion. The majority, 121, of patients with tumour samples were Caucasian, 31 were African and 18 patients were mixed ethnicity or Asian. The EGFR mutation rate was 18% in Caucasians, 23% in Africans and 39% in other races. By histology, 85% of all NSCLC samples tested were confirmed as adenocarcinoma. The EGFR mutation was lower in smokers, overall; smoking status was inversely proportional to the EGFR mutation status ($p = 0.000047$).

First-line treatment of platinum-doublet chemotherapy was administered to 64 patients and 4 patients received TKI. The overall response rate (ORR) was 56%. Second-line treatment of single-agent chemotherapy was administered to 26 patients and TKI were given to 4 patients. The ORR following second-line treatment was 24%. (Chan *et al.* Abstract 3P)

Practice point and future research opportunities

This study of data from a cohort of patients that were mostly non-smoking women with a high proportion of adenocarcinoma demonstrates an EGFR mutation rate consistent with the current incidence reported in most Western countries for patients with NSCLC, suggesting that patients

with NSCLC in South Africa could benefit from targeted treatment approaches, especially non-smokers with adenocarcinoma.

Lower frequency of EGFR and ALK mutations reported for patients with lung adenocarcinoma in the Levant area

Arafat Tfayli and colleagues at the American University of Beirut Medical Center, Beirut, Lebanon conducted an analysis of data from patients with lung adenocarcinoma who were enrolled in a prospective study carried out at 10 centres in Lebanon, Jordan, and Iraq. The study was restricted to patients of Middle Eastern nationality and aimed to establish the prevalence of EGFR and anaplastic lymphoma kinase (ALK) aberrations in this population; EGFR mutations in exons 18-21 were identified by PCR and determination of EML4-ALK translocation was done by the fluorescence in situ hybridization (FISH) Break-Apart test.

Of the 180 patients recruited to date, 120 (67%) are male and 60 (33%) are female with a mean age of 62.6 years. EGFR testing done in 166 patients revealed that 142 (85.6%) patients had EGFR wild type, and EGFR was mutated in 24 (14.4%) patients. Two (1.1%) results are still pending and tissue was insufficient in 12 (6.7%) samples. Of the 115 patients tested for EML4-ALK translocation, 3 (2.6%) patients were positive and negative results were seen in 112 (97.4%) patients. ALK testing could not be carried out in 21 (11.7%) patients and the other results are pending for 6 (3.4%) samples, unattainable due to insufficient tissue in 12 (6.7%) samples or undone because patients were either EGFR or KRAS mutation positive for 26 (14.4%) samples.

The mutation rates were lower in this Middle Eastern population than those recorded in the literature for the Western population; the EGFR mutation rate was 14.4% and the ALK translocation rate was 2.6% in this cohort compared to respective EGFR and ALK rates of 15-20% and 5% reported in the Western literature. (Tfayli *et al.* Abstract 6P)

Practice point and future research opportunities

The frequencies of EGFR mutations and ALK translocations may be lower in patients with lung adenocarcinoma in the Levant area compared to rates reported for the Western population.

Frequency of ALK gene rearrangement in Saudi lung cancer

Also citing the paucity of mutation data for patients with lung cancer in the Middle East, Fouad Hassan Al Dayel, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, presented results from a retrospective study done to establish the frequency of EML4-ALK rearrangements in patients with patients with lung adenocarcinoma in Saudi Arabia.

ALK gene rearrangements were identified in 3 (3%) of 97 lung cancer samples analysed by FISH tissue microarray, using break-apart probes from Vysis (Abbott Molecular, IL, USA) specific for ALK gene rearrangements. Rearrangements were identified in 2 patients with moderately differentiated metastatic lung adenocarcinoma; one patient was a 55 year-old male non-smoker

and the second patient was a 35 year-old male smoker. The third ALK-rearrangement positive sample came from a 21-year old female non-smoker with an incidental lung tumour that was staged after lobectomy as T₁N₂M₀ and characterised as a solid variant of adenocarcinoma. Neither signet cells nor abundant intracellular mucin were observed. Lung carcinoma represents 2.6% of cancer seen at King Faisal Specialist Hospital and Research Centre and 4.5% of cancers in Saudi Arabia as per Saudi Cancer Registry. (Al Dayel, *et al* Abstract 7P)

Practice point and future research opportunities

Incidence of 3% is reported for ALK gene rearrangements in Saudi patients with lung adenocarcinoma, which is similar to the incidence reported for Western populations. ALK gene rearrangement testing can identify patients with adenocarcinoma who are sensitive to ALK inhibitors.

PD1/PD-L1 expression in non-small cell lung tumours differs by localisation, tumour grade and subtype

PD-L1 expression on tumour cells is thought to reflect the immune-checkpoint of the receptor PD-1 on tumour infiltrating lymphocytes (TILs), a mechanism by which tumours escape anti-tumour immune responses. F. Brühl and colleagues from the University Medical Center Freiburg, Freiburg, Germany, investigated PD-L1 and PD1 expression in 484 samples from patients with NSCLC, using immunohistochemical double staining of PD-1 and PD-L1. Tumour expression of PD-L1 was recorded as an H-score, whereas PD-1 and PD-L1 expression on TILs was measured as absolute numbers of TIL per mm².

Significantly increased PD-L1 expression was seen in patients with sarcomatoid tumours (compared with other NSCLC entities $p < 0.001$). PD-L1 was positive in 22.35% of 179 adenocarcinoma samples and 31.16% of 199 squamous cell carcinomas ($p = 0.054$). An association between histological tumour grade (G1-G4) and PD-L1 expression was observed across all NSCLC subtypes evaluated ($p < 0.001$). This association remained significant for only adenocarcinoma following stratification by disease subtype ($p < 0.001$); squamous cell carcinoma did not significantly associate with PD-L1 expression ($p = 0.172$).

PD-L1 expression was seen in TILs, but it was more often co-expressed with PD-1. PD-L1-positive and PD-1-positive/PD-L1-positive TILs showed strong association with general lymphocytic infiltration that was independent of location ($p < 0.001$), whereas PD-1-positive TILs only associated with lymphocytes located in the stroma ($p < 0.001$), (intraepithelial TILs $p = 0.194$). There was a significant association between PD-L1-positive TILs and PD-L1 expression on cancer cells; intraepithelial PD-L1-positive TILs; $r=0.551$ ($p < 0.001$). However, no association was observed between for PD-1-positive TILs and PD-L1 expression on tumours. (Brühl *et al*. Abstract 8P)

Practice point and future research opportunities

PD-L1 expression on tumour cells showed an association across histological subtypes and grades, that was especially strong in adenocarcinoma. Furthermore, PD-L1 expression on NSCLC cells significantly associated with TILs, especially intraepithelial PD-L1-positive lymphocytes. Based on these observations, the authors suggest an autocrine/paracrine loop between NSCLC cells and TILs as being responsible for PD-L1 expression on either cell, thereby providing a possible escape for the tumour from anti-tumour inflammatory responses.

Oestrogen receptor beta is expressed in primary and metastatic lung cancer tumour tissues

Tatiana Bogush, N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation has determined the frequency of the oestrogen receptor (ER) beta expression in NSCLC tumours, and suggest ER beta could serve as a target for adjuvant anti-oestrogen therapy.

The Russian team conducted the study to demonstrate the feasibility of targeting the ER beta in patients with lung cancer and to compare the difference in expression between primary and metastatic tumours to validate ER beta as a prognostic marker for disease progression.

The investigators probed 83 NSCLC and lung metastases surgically obtained tissue samples with primary (clone 14C8, ab288, Abcam) and secondary (F2772, Sigma) antibodies and quantitated expression using flow cytometry. An evaluation by mean cell fluorescence and the number of stained cells using WinMDI software and Kolmogorov-Smirnov approach was done to stratify the samples into one of three groups: high – ER beta positive in more than 50% of cells; moderate – 30 to 49%, and low - expression of ER beta in less than 30% of cells in the sample.

ER beta was expressed in 92% of primary tumours and in 86% of metastatic tumour tissue. The lower mean level of expression between primary and metastatic tumours was 42% and 34%, respectively ($p = 0.03$), with no differences in mean ER beta intensity ($p = 0.06$). High levels of ER beta were found in 35% of NSCLC samples but only 14% of metastatic tissue ($p = 0.03$), and moderate levels were expressed in 65% of primary and 86% of metastatic samples ($p = 0.03$). ER beta was expressed at moderate and high level was similarly in primary and metastatic NSCLC samples at 73% versus 65%, respectively ($p = 0.08$). (Bogush *et al.* Abstract 11P)

Practice point and future research opportunities

Based on these findings of ER beta expression in both primary tumours and metastases, the authors propose that ER beta expression has good prognostic value. Since high and moderate levels of ER beta are expressed in more than half of patients with lung metastases and approximately 70% of patients with primary NSCLC, adjuvant anti-oestrogen therapy may provide clinical benefit in these patients.

Comprehensive analysis by targeted next-generation sequencing of driver mutations in Chinese patients with squamous cell lung carcinomas

Yuankai Shi, Cancer Institute and Hospital, Chinese Academy of Medical Sciences, Beijing, China and colleagues evaluated driver mutation profiles in a large cohort of Chinese patients with squamous cell lung carcinoma to identify highly expressed tumour molecules that could serve as potential drugable targets. The team reviewed 172 formalin-fixed paraffin-embedded samples and detected approximately 2,800 COSMIC mutations from 50 oncogenes and tumour suppressor genes on 159 samples by using Ion Torrent semiconductor-based NGS. They also performed FISH for FGFR1 amplification and immunohistochemistry to detect loss of PTEN expression on 172 samples.

The investigators detected somatic mutations in 73.6% of 159 patients' samples. TP53 was the most often mutated gene in 56.0% of samples, followed by CDKN2A and PI3KCA in 8.8% each of samples, KRAS in 4.4%, and EGFR in 3.1% of samples. The incidence of FGFR1 amplification in 172 patients' samples was 16.9% and loss of PTEN expression was 43.6% (75/172). EGFR mutation occurred at a significantly greater frequency in female and never smokers, while TP53 mutations were significantly more common in men and smokers. The incidence of FGFR1 amplification in current smokers was higher than that in former smokers and never smokers ($p_{\text{trend}} = 0.025$). Loss of PTEN expression was more frequent in the elderly ($p = 0.047$), male patients ($p = 0.033$), patients with early stage disease ($p = 0.042$), and in patients with positive pleural invasion ($p = 0.030$). No significant association was observed between any driver mutation and OS. (Shi *et al.* Abstract 16P)

Practice point and future research opportunities

Nearly three-fourths (73.6%) of Chinese patients with squamous cell lung carcinoma harbour a somatic mutation. There was also high incidence of FGFR1 amplification and loss of PTEN expression. This comprehensive analysis of driver mutations could be used to optimise therapeutic strategies for these patients and guide the development of targeted therapies.

Next generation sequencing provides information on the genetic landscape of squamous cell carcinoma and adenosquamous carcinoma of the lung

Nataliya Chilingirova *et al.* National Center of Oncology-SBALO EAD, Sofia, Bulgaria, presented findings of an analysis of DNA from formalin-fixed paraffin embedded (FFPE) tumour tissue of 13 male and 2 female patients with squamous and adenosquamous lung carcinoma that were participating in a prospective study. All patients had stage IIIB-IV disease that was confirmed as squamous cell carcinoma in 9 patients and adenosquamous carcinoma in 6 patients.

The coding regions of 94 genes and 284 single nucleotide polymorphisms (SNPs) were analysed by sequencing done on an Illumina MiSeq platform using a TruSight Cancer Panel. BaseSpace was used for alignment and variant calling, and VariantStudio was used for further analysis. The effect of rare missense variants, occurring at less than 3% global frequency, was

predicted by RadialSVM and LR scores. Variants were classified as driver mutations, defined as pathogenic mutations associated with cancer development, presumed pathogenic variants that could contribute to cancer growth, and variants with unknown clinical significance.

The investigators identified 243 variants. In squamous cell carcinoma samples, a median 13 (range: 4 to 26) variants per sample were identified and 22 variants (ranged 4 to 57) were detected in adenosquamous carcinoma samples. All patient samples contained loss-of-function variants that included nonsense, frame shift and splice site mutations. The majority, 14 of 15, of these mutations were in haploinsufficient genes. The genes affected in adenosquamous carcinoma samples were ATM, NF1, APC, TP53, BRCA2, APC, CDKN1C, EZH2, and PTEN; in squamous cell carcinoma samples, the relevant genes were NF1, TP53, KIT, XPC, WT1, TSC1, MSH2, and GPC3. According to the authors, the genes identified reveal the role NF1 and TP53 plays in both disease histotypes. (Chilingirova *et al.* Abstract 17P)

Practice point and future research opportunities

Although genetic tests are generally not performed in patients with squamous cell or adenosquamous carcinoma of the lung, findings from this study suggest that molecular profiling by next generation sequencing could be integrated into the disease characterisation of these patients to build a database of potential driver mutations that would enable the discovery of new targets and treatments for patients with squamous cell carcinoma.

PREVENTION AND EPIDEMIOLOGY

BIM deletion polymorphism associates with elevated risk of some lung cancers in a Chinese population

Xia Jin Jing, Respiratory Department, Shanghai Chest Hospital, Shanghai, China studied the association between the 2903-bp deletion polymorphism, which results in lower expression of the proapoptotic protein BCL2-like 11 (BIM), and the risk of lung cancer in the Chinese population. The study enrolled 5698 participants, including 2640 cancer patients and 118 patients with carcinoid tumour.

Logistic regression analysis revealed that individuals harbouring the deletion polymorphism were at higher risk of developing squamous cell lung cancer, odds ratio (OR) 1.64; 95% CI 1.04, 2.53 ($p = 0.028$). Smokers and elderly individuals with deletion polymorphism also showed elevated risk for squamous cell lung cancer, OR=1.72 ($p = 0.042$) and OR 3.10 ($p = 0.003$), respectively. In addition, the deletion polymorphism was significantly associated with the risk of developing squamous cell carcinoma in elderly people, OR 2.02; 95% CI 1.04, 3.78 ($p = 0.033$). However, individuals carrying the deletion polymorphism were found to have a lower risk of adenocarcinoma or large cell lung cancer, OR 0.45; 95% CI 0.21, 0.87 ($p = 0.024$). (Jing *et al.* Abstract 25P)

Practice point and future research opportunities

Individuals in a Chinese population harbouring the BIM deletion polymorphism, especially smokers and the elderly, have a higher risk of developing squamous cell lung cancer but a lower risk of developing adenocarcinoma or large cell lung cancer. Significant risk also associated with squamous cell carcinoma in elderly individuals having the deletion polymorphism.

Initial report of evaluation of data from The Victorian Lung Cancer Registry

Lead investigator Rob Stirling, Alfred Health, Melbourne, Australia presented findings from an evaluation of data prospectively recorded in the Victorian Lung Cancer Registry from patients with clinical or tissue diagnoses of small cell and non-small cell lung cancer. The registry was initiated to collect and assess the management, treatment and outcome of all new cases of lung cancer in order to maintain and improve clinical care through clinical governance provided by steering and management committees. Indicators of patient care and a minimum dataset were selected based upon an extensive literature review and evaluation of established clinical practice guidelines. Outcomes were derived from institutional ICD-10 coding plus follow up and outcome measures that were collected at baseline, 6, and 12 months and 2 and 5 years post diagnosis.

The dataset comprised 690 eligible and consenting lung cancer patients diagnosed from 1 July 2012 to 31 June 2013 at 8 participating Victorian Hospitals (3 public and 3 private metropolitan and 2 regional). Across all 8 institutions, evidence of distress screening was available for 26% of

patients. Diagnosis was confirmed within 28 days of referral in 67% of patients. ECOG status was available in 46% of cases and clinical TNM staging was done for 49% of cases before treatment, with 59% of cases showing a record of multidisciplinary team recommendations. The first treatment was initiated within 42 days from diagnosis in 76% of patients and consisted of curative surgery for 26.5% of patients; less than 5% of patients each received curative chemotherapy and curative radiotherapy. (Stirling *et al.* Abstract 164P)

Practice point and future research opportunities

The evaluation of registry outcomes is useful for the potential identification of targets for providing health care and improving quality. Comparing performance outcomes across institutions and sectors may further identify the need to improve these measures.

CANCER IMMUNOLOGY AND IMMUNOTHERAPY

Immune checkpoints score and CD8-positive T cells infiltration are independent prognostic biomarkers in resected NSCLC

Lead investigator Marta Usó, Department of Medicine, Universitat de València, Valencia, Spain, presented findings from a study that investigated the prognostic role of immune checkpoint expression markers and CD8-positive T cells infiltration in resected NSCLC. The investigators isolated RNA using Trizol from 178 fresh-frozen tumour and normal lung tissue samples and RTqPCR was performed to analyse the expression of CTLA4, PD1 and PDL1; gene expression was normalised against CDKN1B, GUS and ACTB as endogenous control, to derive a gene expression score. The presence of CD8-positive cells was assessed in tumour and stroma compartments in 63 FFPE samples by immunohistochemistry. The positive control was 122 FFPE tumour samples. A multivariate model including CTLA4 and PD1 was created and absolute regression coefficients were used to calculate the immune checkpoints score: $(PD1 \times 0.116) + (CTLA4 \times 0.0589)$; $p < 0.05$ was considered significant.

The tissue analysed was from a cohort of 178 patients, of whom 173 had KRAS mutational analysis showing that 87.9% of patients had wild type and 12.7% of patients had mutated KRAS. The cohort was 86.5% male with a median age of 65 years and 48%, 40.4%, and 11.1% of patients were current, former or never smokers, respectively. Stage I, II, or III disease was reported in 59%, 19.7%, and 21.3% of the cohort. Squamous cell carcinoma was diagnosed in 47.2% of patients, adenocarcinoma in 41.6%, and other types of cancer were seen in 11.2% of patients. Median follow-up in this cohort was 81.23 months (range: 1 to 113 months).

In samples from this patient cohort, a significant association was observed between high immune checkpoints score and CD8-positive infiltrating cells in the tumour compartment ($p = 0.012$). Kaplan-Meier survival analysis showed an association between high immune checkpoints score and longer OS and PFS; patients with high immune checkpoints score demonstrated median OS not reached compared to 40.4 months in patients with low immune checkpoints score ($p = 0.008$). Better PFS of 82.6 versus 23 months was also associated with patients having high and low immune checkpoints score, respectively ($p = 0.009$). The presence of CD8 cells in the tumour compartment significantly associated with better survival; patients with CD8-positive cells had OS of 73.9 versus 40.4 months in patients with low levels ($p = 0.021$) and PFS was 56.8 compared to 23 months in patients with high and low levels of CD8-positive tumours, respectively ($p = 0.026$). Upon multivariate analysis, immune checkpoints score and CD8-positive cells infiltration were identified as independent biomarkers of prognosis; high versus low immune checkpoints score, HR 0.527 ($p = 0.001$) and CD8-positive cell infiltration positive versus negative, HR 0.386 ($p = 0.004$). (Usó *et al.* 39PD)

Practice point and future research opportunities

The immune checkpoints score based upon CTLA4 and PD1 expression levels developed in this study and also the presence of CD8-positive cells in the tumour compartment provided

relevant prognostic information for a better characterisation of early-stage NSCLC, including which patients may be candidates for immune-based therapies.

Patients with advanced, refractory squamous non-small cell lung cancer show benefit from nivolumab

Lead investigator Gérard Zalcman, CHU de Caen, Caen, France and colleagues compiled results in a poster from a phase II trial of nivolumab, an anti-programmed death-1 (PD-1), immune checkpoint inhibitor in patients with squamous non-small cell lung cancer (squamous NSCLC) that had been refractory to 2 or more prior treatments. Most (64.9%) patients had ≥ 3 prior treatments, 90% of patients had received their last treatment within 6 months of study entry, and 92% of patients were current or former smokers. Nivolumab at 3 mg/kg every 2 weeks was administered to 117 patients until progression or unacceptable toxicity. The primary endpoint, confirmed objective RR assessed by an independent radiology review committee (IRC) per RECIST v1.1, was met.

At a minimum follow-up of 11 months, the IRC-assessed ORR was 15%, with 17 patients demonstrating a response. The median time to response was 3 months (range: 2 to 9 months). The median duration of response had not been reached by conference date (range: 2+ to 12+ months) and the response is ongoing in 76% of responding patients.

Objective responses were observed across all subgroups including age and prior therapies. The ORR for patients < 65 , ≥ 65 and < 75 , and ≥ 75 was 12.1%, 20.9% and 6.3%, respectively. The ORR for patients receiving 2, 3 and ≥ 4 prior systemic therapies was 9.8%, 17.3% and 16.7%, respectively. The ORR by PD-L1 status, defined as $\geq 5\%$ of tumour cells with cell surface staining, was 24% for patients with PDL-1 positive tumours compared to 14% in patients with PDL-1 negative tumours. Stable disease was achieved by 26% of patients and the median duration was 6 months. The PFS rate, a secondary endpoint, was 20% at one-year; 95% CI 13%, 29%, and median PFS was 2 months; 95% CI 2, 3. The median follow-up for OS was 8.0 (range: 0.0 to 17.3) months and median OS was 8.2 months for all nivolumab treated patients (95% CI 6.1, 10.9 months). The one-year OS rate was 40.8% (95% CI 31.6, 49.7).

Treatment-related adverse events (AEs) grades 3 or 4 were reported in 17% of patients and consisted of fatigue in 4%, pneumonitis in 3%, and diarrhoea in 3% of patients. One patients died of pneumonia and one patients died of ischemic stroke, which were determined to be treatment-associated and occurred in patients that were experiencing progressive disease and also had multiple comorbidities. (Zalcman *et al.* Abstract 104PD)

Practice point and future research opportunities

Nivolumab immunotherapy provided clinical benefit in patients with squamous non-small cell lung cancer. Nivolumab-related adverse events were manageable in this cohort of patients with advanced disease that was refractory to previous therapy. PD-L1 staining as a biomarker is an interesting concept that is clearly of interest to other anti-PD-1/PD-L1 datasets; however, there remains a need for standardisation and validation.

TG4010 immunotherapy combined with first-line chemotherapy improves outcome compared to placebo in patients with advanced non-small cell lung cancer. Results from the phase IIb part of the TIME study

Elisabeth Quoix, Nouvel Hopital Civil, Strasbourg, France and colleagues reported findings from the TIME trial, which was done to confirm TrPAL as predictive of clinical activity for TG4010, a novel immunotherapy product consisting of a poxvirus (MVA) altered to code for MUC1 tumour-associated antigen and interleukin-2. TG4010 administered in combination with chemotherapy demonstrated safety and efficacy in patients with advanced NSCLC, and findings from one study suggest that having a normal level of Triple Positive Activated Lymphocytes (TrPAL, CD16+CD56+CD69+) at baseline may be a predictive biomarker for TG4010 efficacy.

TIME is a double blind randomised phase IIb/III study comparing the combination of first-line chemotherapy plus either TG4010 or placebo. A total of 221 patients with stage IV NSCLC, previously untreated for advanced disease, were enrolled in the phase IIb portion of the trial, which has a primary endpoint of prospective validation of the TrPAL predictive biomarker; other endpoints included the safety and efficacy by PFS of TG4010 in combination with chemotherapy in this patient population.

The lowest baseline level of TrPAL at screening was seen in 152 patients who demonstrated PFS HR of 0.66; 95%CI 0.46, 0.96, compared to patients with high baseline levels of TrPAL ($p = 0.014$).

Subgroup analysis of 195 patients with non-squamous tumours and low TrPAL ($< Q3$) demonstrated a statistically significantly improved median PFS of 5.9 months (95%CI 0.55, 8.3) in 64 patients receiving TG4010 versus 4.9 (95%CI 4.2, 5.9) in 67 patients receiving placebo; HR 0.60. Median OS in this cohort was 14.9 months (95%CI 11.1, NA) with TG4010 versus 10.4 (95%CI 8.1, 14.1) with placebo; HR 0.70

Normal TrPAL levels at baseline were recorded for 177 patients and 170 patients (85 per treatment arm) comprised the ITT population. PFS events were reported for 70 (82.4%) TG4010 and 74 (87.1%) placebo patients; HR 0.74; 95%CI 0.53, 1.02; the 98.6% posterior probability of HR was < 1 , passing the threshold of 95% necessary to meet the efficacy endpoint in patients with normal TrPAL.

Patients with normal TrPAL receiving TG4010 demonstrated median PFS of 5.7 (95% CI 4.4, 6.4) months versus 5.1 (95%CI 4.2, 5.9) months with placebo; HR 0.78 (95%CI 0.55, 1.10). Median OS was 12.8 (95% CI 9.7, 17.9) months versus 10.5 (95%CI 8.9, 14.1) months with placebo; HR 0.85 (95%CI 0.57, 1.27). The RR was 37.6% versus 30.6% in placebo patients; the duration of response was 31.0 (range: 19.9 to 53.7) weeks versus 18.7 (range: 13.4 to 30.3) weeks in the respective groups. Results are pending for the cohort with high TrPAL.

TG4010 related adverse events were mostly mild or moderate injection site reactions that were reported by 31% of patients receiving TG4010. (Quoix *et al.* abstract 105PD) This trial was sponsored by Transgene SA

Practice point and future research opportunities

Findings from the TIME trial confirm the efficacy and safety profile of TG4010 in patients with stage IV non-small cell lung cancer. TG4010 showed enhanced efficacy in patients with non-squamous tumours and a low baseline level of TrPAL associated with improved outcome. There were a reasonable number of patients for a phase IIR study, wherein the primary endpoint (probability that TG4010 improves PFS (HR<1) is more than 95%) was achieved in patients with normal TrPAL levels. These findings support continuing the TIME study in phase III.

Novel imprime PGG given first-line in combination with bevacizumab carboplatin and paclitaxel shows benefit for patients with advanced non-small cell lung cancer

Ada Braun, Biothera, Eagan, USA, and colleagues in the USA and Germany compiled findings in a poster from a phase II randomised trial of a novel innate immune modulator, Imprime PGG[®], in patients with previously untreated stage IV NSCLC. Imprime PGG aids the innate immune system in killing cancer cells and it has been found to act synergistically with anti-tumour monoclonal antibodies tested to date. This trial randomised patients 2:1 to receive Imprime PGG[®] at 4 mg/kg four times weekly, together with carboplatin/paclitaxel plus bevacizumab (treatment arm) or bevacizumab plus carboplatin/paclitaxel (control arm) for 4 to 6 cycles; patients in the control arm were treated until documented progression or intolerable toxicity occurred. At the time of the primary analysis, all patients in both arms had either progressed or completed a minimum of 18 treatment cycles.

Data were evaluable for 48 and 23 patients in the treatment and control arms, respectively. The trial met its primary endpoint by demonstrating improvement in ORR over control; ORR was 60.4% in the treatment arm with one patient achieving complete response (CR) and 28 patients demonstrating partial response (PR) versus an ORR of 43.5% in the control arm wherein no CR and 10 PR were observed ($p = 0.21$). More favourable outcomes were also reported with imprime PGG over control for the secondary endpoints, including duration of response (DoR), OS and safety. The DoR was nearly doubled with imprime PGG versus control; median DoR was 10.3 months in the treatment arm compared to 5.6 months with control. However, no significant improvement in PFS was demonstrated; median PFS was 11.9 months versus 10.2 months in the treatment versus control arms, respectively; hazard ratio (HR) 0.84 ($p = 0.54$). Median OS was 16.1 months versus 11.6 months in the treatment and control arms, respectively, HR 0.66 ($p = 0.13$). Imaging assessments of the chest and abdomen done by computed tomography every six weeks showed continued regression of lesions with maintenance treatment with imprime PGG plus bevacizumab and chemotherapy.

Similar incidence of adverse events (AEs) was seen in both treatment groups. AEs leading to study discontinuation occurred in 37.3% and 43.3% of patients in the treatment and control arms, respectively. AEs that were determined to be possibly or probably related to PGG by the investigator consisted of chills, reported by 13% of patients and dyspnoea and fatigue, each reported by 10.2% of patients; in addition, 8.5% of patients each reported nausea, pyrexia, or infusion-related reactions. (Braun *et al.* Abstract 112P) The trial was sponsored by Biothera.

Practice point and future research opportunities

Further evaluation of first-line Imprime PGG in combination with bevacizumab and carboplatin/paclitaxel chemotherapy is warranted since patients with advanced NSCLC demonstrated numerical increases in overall response rate, duration of response, progression-free survival and overall survival versus control.

EARLY STAGE AND LOCALLY-ADVANCED NSCLC

Mutational status in patients with resected non-small cell lung cancer is prognostic for outcome

Stéphane Renaud, Thoracic Surgery, CHU Strasbourg-Nouvel Hopital Civil, Strasbourg, France, and colleagues reviewed data from 1971 patients completing molecular testing for NSCLC from January 2007 to December 2012, and included data from 841 patients also having a surgical specimen in this retrospective review. They evaluated whether EGFR and KRAS mutational status could be useful biomarkers to better identify patients at risk for early disease recurrence following surgically treated NSCLC.

Comparisons between groups of patients with different mutational status were done using Chi-2, student t, and Fisher test, whereas Kaplan-Meier and Cox proportional hazard models were used to assess the impact of variables on OS and disease-free survival (DFS). Significance for p values was determined at ≤ 0.05 .

EGFR mutation was observed in 103 (12.2%) patients and KRAS mutation was detected in 265 (31.5%) patients. EGFR mutation group significantly associated with non-smoking status and female gender ($p < 0.0001$), whereas KRAS mutation associated with active smoking ($p = 0.02$). Both median OS and DFS were significantly lower for patients with KRAS mutation compared to EGFR mutation and wild type patients; OS for KRAS mutation was 43 months, compared to EGFR mutation of 67 months, and 55 months for patients with wild-type EGFR ($p < 0.0001$ for all OS comparisons). DFS was 19 months for KRAS mutation compared to 24 months for both EGFR mutation and EGFR wild-type patients ($p = 0.02$ for all DFS comparisons).

Patients with KRAS G12V transversion demonstrated the worst OS and DFS compared to patients in all other subtypes; OS with KRAS G12V transversion was 26 months compared 60 months for all other patients ($p < 0.0001$). DFS was 15 months in patients with KRAS G12V transversion compared to 24 months in all other patients ($p < 0.0001$). Multivariate analysis confirmed this finding; OS in patients with non-G12V status was HR 0.43 ($p < 0.0001$) and DFS in this cohort was HR 0.67 ($p = 0.01$). Local and/or distant recurrence was observed in 52.2% of non-G12V patients compared to 100% of patients with G12V ($p < 0.0001$). (Renaud *et al.* Abstract 65P)

Practice point and future research opportunities

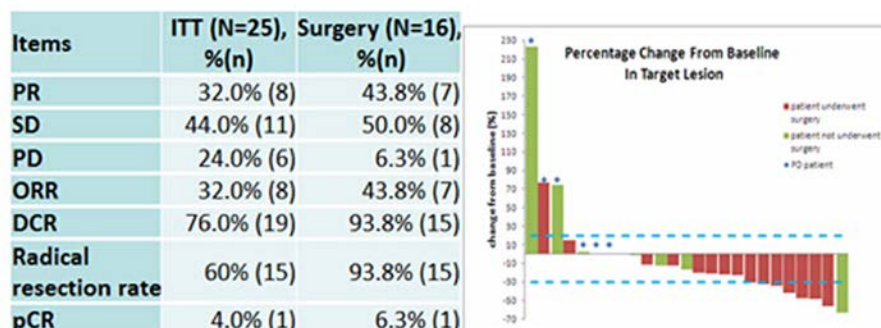
KRAS mutation and EGFR mutation are molecular biomarkers that seems to be predictive of survival and recurrence in patients with early stage NSCLC; the poorest overall and disease-free survival as well as the highest incidence of postsurgical recurrence significantly associated with KRAS G12V transversion mutation.

Efficacy and safety results of neo-adjuvant erlotinib in patients with stage IIIA-N2 non-small cell lung cancer and activating EGFR mutation: Phase II trial results

Baohui Han, Pulmonary Department, Shanghai Chest Hospital, Shanghai, China presented findings from a single arm, phase II clinical trial that evaluated the efficacy and safety of erlotinib given as neoadjuvant treatment in patients with stage IIIA-N2 NSCLC and activating EGFR mutation. The trial's primary endpoint was radical resection rate. Secondary endpoints included pathological complete response (pCR), ORR, DFS, OS, safety profile, and explorative biomarkers. After screening of 155 patients, 44 patients with IIIA N2 NSCLC and 25 patients with IIIA N2 NSCLC plus activating EGFR (exon 19 or 21) mutations were enrolled. All patients were treatment naive and had ECOG performance status 1, stage IIIA-N2 NSCLC, which was confirmed by endobronchial ultrasound. During the 56-day neoadjuvant phase, all patients received erlotinib 150 mg orally per day; patients showing benefit from erlotinib and evaluated as resectable following the neoadjuvant treatment phase underwent surgery.

The response and disease control rates were 32% and 76%, respectively. In all, 16 patients were evaluated as resectable and underwent surgery; R0 resection was performed in 15 (93.8%) patients, which yielded a resection rate of 60%. The pCR was 6.3% and the pathological resection rate was 93.7%. Following surgery, patients received long-term follow-up including a quarterly chest CT scan for up to 2 years. The post-surgical median DFS (from operation) was 10.4 months. The OS data are not yet mature.

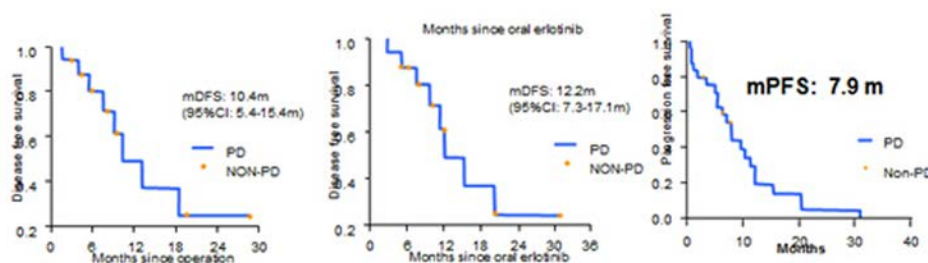
Results: Response and Radical resection rate



Median duration from the surgery to discharge is 8(3-15) days

DFS and PFS

Adj chemo(cycles)	0	1	2	3	4	5	6
Patient No.	2	3	2	6	1	1	1



Caption: Erlotinib as neoadjuvant treatment in endobronchial ultrasound confirmed stage IIIA-N2 NSCLC patients with EGFR mutation (exon 19 or 21), ESTERN: A prospective, single arm, phase II clinical trial. © Baohui Han

EGFR mutation status remained unchanged before and after the surgery in most patients with the exception of 3 patients with an exon 19 deletion that changed to EGFR wild-type after resection.

Few adverse events were reported with erlotinib and most were mild; 7 (28%) patients had grade I-II rash and one (4%) patient each had grade I diarrhoea, and abnormal liver function. One patient experienced a serious adverse event, cerebral infarction, while receiving neoadjuvant erlotinib. (Han *et al.* Abstract 81O)

Practice point and future research opportunities

Neoadjuvant erlotinib showed promise in this study for treatment of patients with EGFR mutant, stage IIIA-N2 NSCLC; most patients were evaluated as eligible for surgical resection of tumours.

However, the study authors presumed that induction therapy in EGFR mutation positive stage IIIA-N2 NSCLC patients is comparably as effective for downstaging and downsizing as induction chemotherapy. Never smoker and women seem to have the most benefit from this approach. However, PFS and DFS results are not yet convincing. It may be more suitable to investigate this approach in a setting restricted to common mutations in never smokers and women than to investigate it in a curative setting unselectively. The best time and schedule of adjuvant/neoadjuvant chemotherapy in this setting is currently unknown and chemotherapy has been actually proven to be curative.

Surgical salvage of local recurrences after stereotactic ablative radiotherapy in patients with early-stage NSCLC performed with limited post surgical complications

Naomi Versteegen, Department of Radiation Oncology, Vrije University Medical Centre, Amsterdam, The Netherlands and colleagues analysed records from the Vrije University Medical Centre, containing data of stereotactic ablative radiotherapy (SABR) done at this institution. Their study aimed to identify risk factors for disease recurrence in order to determine the optimal SABR follow-up regime.

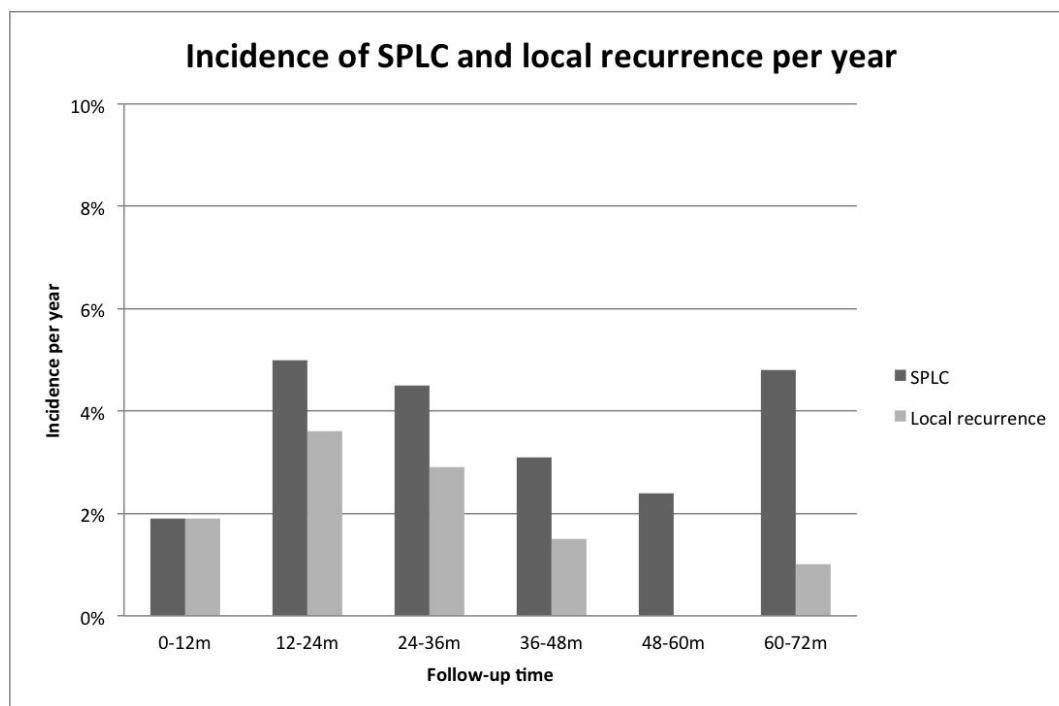
SABR is a guideline-recommended treatment for early stage NSCLC that has been associated with local control rates of $\geq 90\%$. Data of patients having received prior treatment for the index tumour, having double tumours, or presenting with disease TNM-stages other than T1-T2N0M0 were excluded from the analysis. SABR was performed at the recommended minimal biologically effective dose (BED₁₀) of 100Gy (ESMO Clinical Practice Guidelines 2013).

Local recurrences were diagnosed in 46 of the 855 patients following SABR within follow-up of median 52 months. Actuarial local control rates were 92.4% and 90.9% at 3 and 5 years respectively, and the median time to local recurrence was 22 months (range: 7 to 87 months). The diagnosis of local recurrence was made on computed tomography (CT) scans in 44 patients, confirmed by pathology in 18 (39%) patients and/or FDG-PET scans in 32 (70%) patients. Recurrence was local in 25 (54%) patients and loco-regional in 31 (67%) patients. During the first year the incidence of second primary lung cancer and local recurrences per year was similar at just under 2%; however, the incidence of second primary lung cancer increased over time to nearly 5% between 60 to 72 months, whereas the incidence of local recurrence decreased to approximately 1% during this time. The highest incidence of local recurrence was seen between 12 and 24 months.

Cox regression analysis revealed no significant association between any of the investigated parameters with local failure.

Since 74% of patients with local recurrence were initially considered inoperable, just 10 (21%) of patients experiencing local recurrence were given radical salvage therapy; of these 6 patients underwent surgery plus adjuvant chemotherapy, 3 patients had surgery plus radiotherapy, and one patient underwent surgery plus chemo-radiation. The median survival was 13 months in all

patients following diagnosis of a local recurrence, and the 2-year survival rate was 23%. Patients undergoing radical salvage achieved median OS of 36 months following local recurrence diagnosis, and median OS after surgery was 38 months with a median follow-up of 40.6 months.



Caption: Figure displaying the incidence of second primary lung cancer (SPLC) and local recurrences per year in a large cohort of patients treated with SABR for early stage NSCLC. © Naomi Versteegen

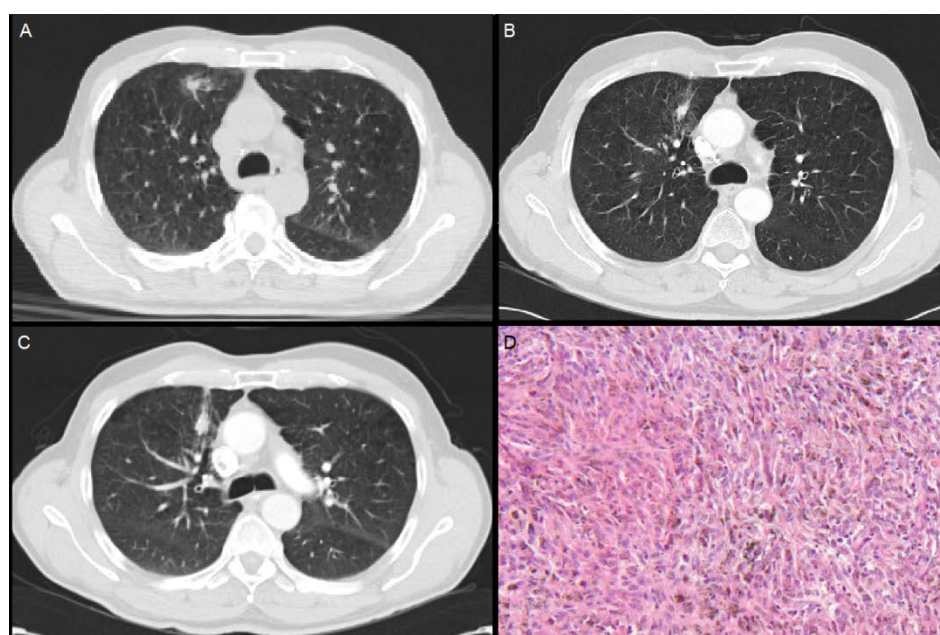
Two post surgical grade II complications by Clavien-Dindo classification were reported. Also, 2 patients had a persistent air leakage that was treated with a thoracic tube (grade IIIa). The 30-day mortality rate was 0% and the median length of hospital stay was 7 days. Mediastinal metastases were detected in 3 patients by lymph node dissection and treated then with adjuvant therapy. (Versteegen *et al.* 600)

Practice point and future research opportunities

Analysis of data from a relatively large cohort of patients with a local recurrence following SABR for early stage NSCLC revealed that none of the investigated factors correlated with local failure, which was most likely to occur between 12 and 24 months. Long-term follow-up is recommended after SABR for monitoring the treated area and discovering new primary tumours.

Outcome following surgical salvage for local failures following stereotactic ablative radiotherapy

Naomi Verstegen *et al.* Department of Radiation Oncology, Vrije University Medical Centre, Amsterdam, The Netherlands, reported their experience with salvage surgery in 7 patients who developed a local recurrence after SABR that were recorded in the Vrije University Medical Centre database. The patients all had peripheral pulmonary lesions; one patient each had extensive adhesions and limited adhesions. Median time to local recurrence following SABR was 27.6 months; diagnoses of local recurrence were based on CT- and FDG-PET-scans and 4 patients had a pathological diagnosis of recurrence prior to surgery. The resection specimen of all patients contained viable tumour cells.



Caption: Example of patient with local recurrence following SABR for NSCLC. A: CT-scan at the time of diagnosis of the primary tumour. B: CT-scan one year after SABR. C: CT-scan at the time of local recurrence. D: Histological specimen of this patient showing poorly differentiated tumour cells (100x enlarged). © Naomi Verstegen

Following surgery, which included lobectomy in 4 cases, sleeve-lobectomy, wedge resection, and pneumonectomy in one case each, two grade II complications by Clavien-Dindo classification were observed. Also, one patient had a persistent air leakage treated with a thoracic tube (grade IIIa). The 30-day mortality rate was 0% and the median length of hospital stay was 7 days. Mediastinal metastases were detected in 3 patients by lymph node dissection who were then given adjuvant therapy. The median OS after surgery was 38 months with a median follow-up of 40.6 months. (Verstegen *et al.* 610)

Practice point and future research opportunities

This experience with surgical salvage for post-SABR local recurrence demonstrated a single grade IIIa and a 30-day mortality of 0%, suggesting that salvage surgery can be safely performed in selected patients. For operable patients, surgery remains the standard of care. For “inoperable” patients, multidisciplinary evaluation/discussion should be in place and involve the surgeon. Inoperability is not the same for everyone. Clinical stage I cancer does not always translate into pathological stage I cancer. For solid pericentimeter lesion, 10% are found to have nodal involvement after good surgery. The larger the tumour, the higher is the risk of nodal involvement. A proportion of these patients with node positive disease may have a poor outcome while another proportion may benefit from the nodal resection with or without adjuvant chemotherapy.

No statistically significant difference between clinical outcome following surgery or stereotactic radiotherapy in patients with stage I non-small cell lung cancer: Results from propensity score analysis

Sahar Mokhles, Erasmus University Medical Center, Rotterdam, The Netherlands and colleagues conducted an analysis that compared patient outcomes following lobectomy or SABR, the two current guideline-specified treatments for clinical stage I NSCLC. The investigators pointed out that findings from prospective randomised clinical trials comparing these modalities are scarce in the literature, leading them to compare these two cohorts using a propensity-score matched analysis comparing two similar groups to determine the patient outcomes with each treatment. Data were reviewed from 577 patients with clinical stage I NSCLC; 96 patients received open lobectomy at Erasmus University Medical Center in Rotterdam and 481 were treated with SABR at Vrije University Medical Center in Amsterdam. Toxicity and complications were scored according to Common Terminology Criteria for Adverse Events version 4.0.

Matching of patients according to propensity score yielded two cohorts comprising 73 patients in each treatment group. Median follow-up for surgical patients was 49 months compared to 28 months for SABR patients. The OS in patients who underwent surgery was 95% and 80% at 12 and 60 months, respectively, versus 94% at 12 months and 53% at 60 months in the SABR cohort. Locoregional control up to 60 months post procedure was similar between the two cohorts, although a trend toward better locoregional control was seen in the surgery patients.

Evaluation of data from the patients receiving SABR revealed no treatment-related deaths and just one patient experienced grade 3 late side effects. One patient died due to renal failure and infection with *Pseudomonas* in the lobectomy cohort and 5 patients required intervention for adverse events.

The investigators noted a trend towards improved OS favouring patients treated surgically after 3 years; however, no statistically significant difference in OS was observed between treatment cohorts ($p = 0.089$). (Mokhles *et al.* Abstract 63PD)

Practice point and future research opportunities

Patients with stage I NSCLC treated either surgically or with SABR demonstrated similar OS at 12 and 60 months, although the median follow-up times were different for the two cohorts. Additional information that would be helpful to interpret this trial would be the number of T1 in the surgical stage I, the concordance rate between clinical and pathological stages in the surgical group, and how post treatment loco-regional recurrence was assessed. However, a trend toward improved survival with surgery after three years of follow-up that did not reach statistical significance warrants further study. Evaluation should be extended to 90 days, since there are reports of twice the mortality after pneumonectomy if the 90-day limit is considered.

ADVANCED NSCLC

Patients with EGFR-TKI-resistant advanced non-small cell lung cancer show durable response to novel AZD9291

Updated results from the AURA study, a global multicentre phase I trial of AZD9291 in patients with EGFR mutation positive advanced NSCLC, were presented by lead investigator Pasi Jänne, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, USA. AZD9291 selectively and irreversibly targets the EGFR and has activity against both EGFR-TKI-sensitising and resistance (T790M) mutations.

AURA enrolled 283 patients with EGFR mutation positive advanced NSCLC and acquired resistance to EGFR-TKI, including patients with stable brain metastases. The median patient age was 60 years and 62% were female, 61% were Asian and 31% of patients were Caucasian. Prospective T790M testing was optional for 31 patients enrolled in a dose escalation cohort but required for 252 patients in the expansion cohort. The majority of patients (62%) had received EGFR-TKI therapy immediately prior to study entry. T790M positive tumours were confirmed in 163 patients by central testing. Both cohorts received AZD9291 orally at doses of 20 to 240 mg once daily. The primary aim of study was to evaluate safety, tolerability and efficacy expressed as ORR. Secondary objectives included assessment of anti-tumour activity by DoR, PFS and efficacy endpoints by independent central review.

Responses according to RECIST v1.1 criteria were observed at all dose levels; the investigator-assessed confirmed ORR was 59% for patients with EGFR T790M-positive tumours and the ORR was 23% in patients with T790M-negative tumours.

The ORR at the recommended phase II dose of 80 mg of AZD9291 orally was 66%. The median DoR had not been reached at the time of analysis, with the longest DoR being greater than 8 months in patients with EGFR T790M-positive tumours. Also noted as immature, median PFS in this cohort was 10.9 months. The independent centrally reviewed data showed that patients with EGFR T790M-positive tumours receiving 80 mg daily of AZD9291 demonstrated an ORR of 54%; the immature median DoR was 12.4 months and immature median PFS was 13.5 months.

The most common adverse events with AZD9291 treatment were primarily low-grade diarrhoea and rash that was reported by 50% and 46% of patients, respectively. Grade 3/4 investigator determined treatment related adverse events occurred in 17% of patients. (Jänne *et al.* LBA3)

Practice point and future research opportunities

Response rate and duration of response results from this phase I trial suggest that AZD9291 may be an effective treatment in patients with advanced NSCLC and tumours with acquired resistance to EGFR-TKI that are either T790M positive or T790M negative, a positive finding since T790M mutation eventually occurs in approximately 60% of patients. AZD9291 was also

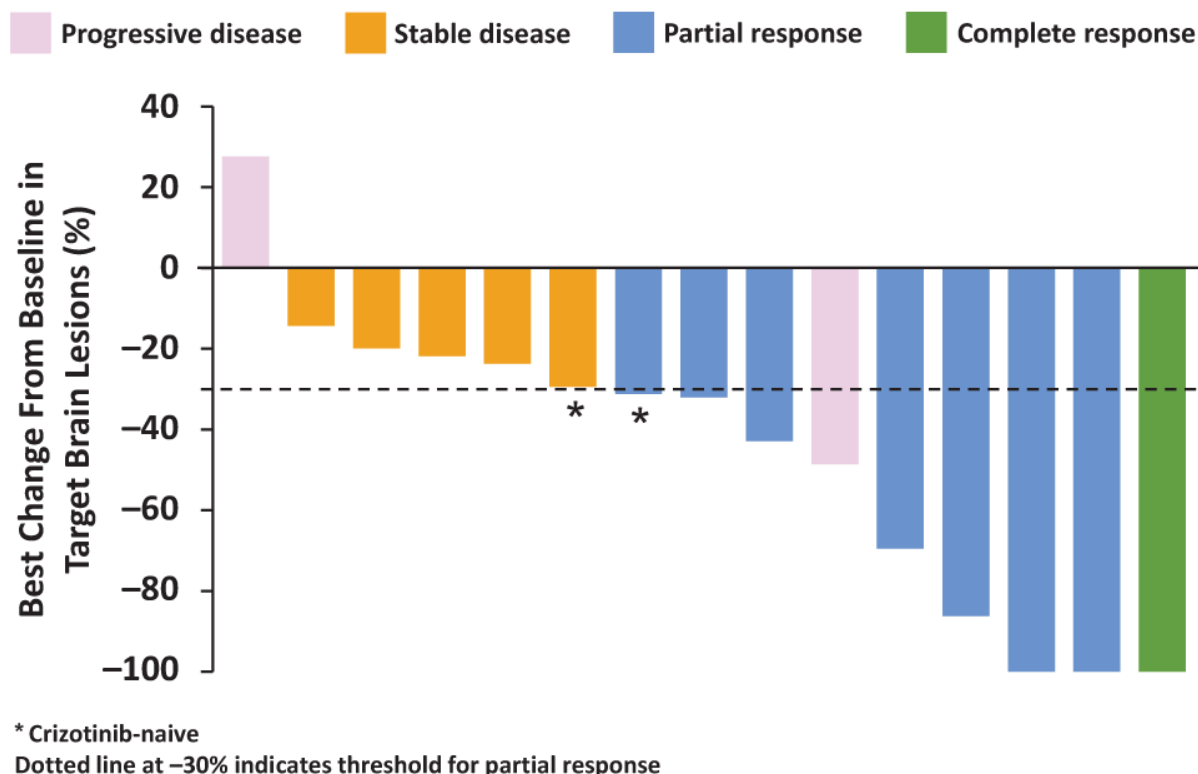
well tolerated, unlike currently available EGFR TKIs wherein treatment may be limited by cutaneous toxicity and severe diarrhoea in patients with wild-type EGFR.

Brigatinib demonstrates intracranial anti-tumour activity and durable response in patients with brain metastases following crizotinib treatment for non-small cell lung cancer

Noting that central nervous system (CNS) progression has been observed in a number of patients treated with crizotinib for ALK-positive NSCLC David Kerstein, Clinical Research, ARIAD Pharmaceuticals, Inc., Cambridge, USA presented findings from a post hoc analysis of data from ALK-positive NSCLC patients with intracranial CNS lesions participating in a phase I/II single-arm, multicentre study of brigatinib. Brigatinib is an oral TKI that has demonstrated preclinical activity against a range of crizotinib-resistant mutations, including ALK, which received breakthrough therapy designation by the US Food and Drug Administration in 2014.

Brigatinib was given to patients with advanced malignancies at a dose of 30 to 300 mg orally once daily. Contrast-enhanced MRIs of the brain were taken at baseline and at follow-up, and centrally reviewed by blinded independent neuroradiologists. Lesions having a longest diameter of 10 mm or greater were defined as measurable lesions. In this post hoc analysis, up to 5 measurable intracranial CNS metastases could be chosen as target lesions by the independent reviewers. Intracranial response (including PFS and DoR) was defined using criteria based on RECIST. The post hoc analysis was done on data from 45 of the 49 patients identified with baseline brain metastases that had evaluable data at cut-off. The patients were among participants in a larger study of brigatinib in patients with advanced malignancies.

The patients identified with baseline brain metastasis with evaluable data were on study a median of 56.1 weeks. Measurable brain metastases were reported for 15 patients and non-measurable brain metastases for 30 patients. In 45 patients overall with brain involvement and a follow-up scan, an ORR following treatment of 53% and 30% was seen in patients with measurable and non-measurable brain metastases, respectively. In patients with measurable and non-measurable brain metastases, one and 9 patients achieved complete response and 7 and NA patients achieved partial response, respectively. Stable disease was reported for 2 and 4 patients with measurable and non-measurable lesions, respectively, and progressive disease occurred in 2 and 4 patients in the respective groups.



Caption: Brigatinib activity in ALK-positive NSCLC patients with measurable intracranial CNS metastases (n=15) in a phase 1/2 trial. Objective response was achieved by 8/15 (53%) patients. © David Kerstein

In all patients with brain metastases, the median intracranial PFS was 97 weeks and the median duration of intracranial response was 82 weeks in 16 patients with a response and a follow-up scan. Intracranial response was reported for 6 patients with measurable brain metastases and for 8 patients with non-measurable lesions. Intracranial disease control was achieved by 10 patients with measurable and by 22 patients with non-measurable brain metastases.

Treatment-emergent adverse events were mild to moderate in severity and included nausea, diarrhoea, and fatigue, which were reported by 24 (52%), 24 (52%) and 23 (50%) patients, respectively. (Kerstein *et al.* Abstract LBA4) The study received sponsorship from ARIAD.

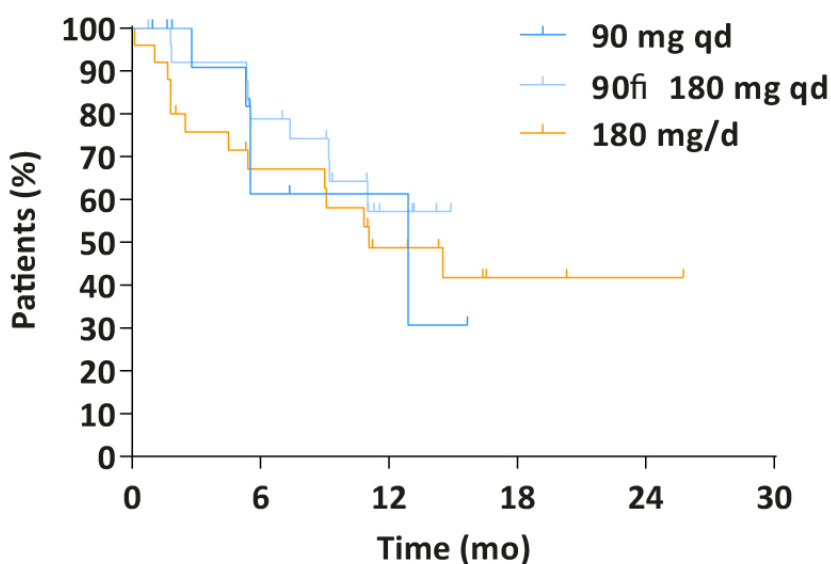
Practice point and future research opportunities

This second-generation ALK inhibitor is characterised by a high response rate in patients with measurable and non-measurable brain metastasis and penetration into the central nervous system. Brigatinib demonstrated significant intracranial antitumour activity in ALK-positive NSCLC patients with brain metastases who also demonstrated durable responses. A prospective evaluation of brigatinib in patients with ALK-positive NSCLC and brain metastases has begun as part of the ongoing phase II ALTA study.

Efficacy and safety of brigatinib in patients with advanced malignancies, including ALK-positive non-small cell lung cancer at selected dose levels

Rafael Rosell, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Spain, reported on the clinical activity of AP26113, an investigational oral ALK inhibitor that had shown preclinical activity against native ALK and a broad range of crizotinib-resistant mutants. He headed an international team in conducting a phase I/II trial to determine dose levels for continued evaluation of AP26113 in a phase II trial. This single-arm, multicentre study evaluated AP26113 at total daily doses from 30 to 300 mg in patients with advanced malignancies. Prof. Rosell presented safety and efficacy findings from an analysis of AP26113 at three dose levels given daily.

By 4 August 2014, the trial had enrolled 137 patients; 79 patients had ALK-positive NSCLC and 71 (90%) of these patients had received prior treatment with crizotinib. The ORR in 60 evaluable patients was 79%, 81%, and 68% in the 90 mg, 90 to 180 mg, and 180 mg cohorts, respectively. Of the 14 patients receiving AP26113 at 90 mg, no CR was seen; 11 (79%) patients had a PR, 1 (7%) patient had stable disease (SD) and no patient experienced progressive disease (PD). Of the 26 patients receiving AP26113 in the 90 to 180 mg cohort, 3 (12%) patients had CR, 18 (69%) patients achieved PR, 2 (8%) patients had SD and PD was observed in one (4%) patient. In 25 patients receiving AP26113 in the 180 mg cohort, there were two (8%) CR, 15 (60%) PR, 3 (12%) patients had SD, and PD was observed in 5 (20%) patients. Median PFS was 12.9 month in patients receiving the lowest dose of AP26113. Median PFS had not been reached in the 90 to 180 cohort and the median PFS in patients in the 180 mg cohort was 11.1 months.



Caption: Progression-free survival (PFS) with brigatinib by selected dosing regimens in ALK-positive NSCLC patients in a phase 1/2 trial. Median PFS was 12.9 month for 90 mg qd (n=14), not reached for 90 mg qd escalated to 180 mg qd after 7 days (90→180 mg qd; n=26), and 11.1 month for 180 mg/d (n=25). © Rafael Rosell

Across these three cohorts, the most common adverse events were mostly grade 1 or 2 and included nausea, diarrhoea, and fatigue; these were reported by patients across all three respective dose cohorts. Adverse events of grade ≥ 3 included increased lipase, neoplasm progression and increased amylase. Grade ≥ 3 adverse events included dyspnoea, hypoxia, and new pulmonary opacities suggestive of pneumonia or pneumonitis occurred within 7 days of starting brigatinib (usually within 24–48 hours), required medical intervention and occurred at lower rates with lower doses. Early-onset pulmonary symptoms were observed in 4% of patients in the 90 mg cohort and in 14% of patients receiving 180 mg. None of the patients receiving the 90 mg dose that was escalated to 180 mg demonstrated early-onset pulmonary symptoms. (Rosell *et al.* Abstract 990)

Practice point and future research opportunities

Similar efficacy was seen across all dose levels of AP26113 evaluated in this study; however fewer patients with advanced ALK-positive NSCLC showed early-onset pulmonary symptoms in the 90 mg and 90–180 mg cohorts; these dose levels are being further assessed in the phase II ALTA trial of AP26113 in patients with ALK-positive NSCLC that are resistant to crizotinib.

Since resistance to ALK inhibitors in half of the cases is related to ALK dependence, and in other half to other pathways, it might be necessary to perform molecular testing at progression on first generation ALK inhibition therapy and then administer the second-generation inhibitor. The open questions to be addressed in the future are drug activity, particularly in the CNS, and coverage of resistance mechanisms, toxicity profiles and cost issues.

Dacomitinib may improve progression-free survival over erlotinib in patients with advanced non-small cell lung cancer and EGFR mutations: Findings from an ARCHER 1009 subset analysis

Lead investigator Luis Paz-Ares, Hospital Universitario Virgen del Rocío, Seville, Spain, pointed out that no randomised comparisons of EGFR TKIs in EGFR mutated NSCLC have been done to date. Together with colleagues, he conducted a phase III trial that directly compared dacomitinib to erlotinib in patients with advanced/metastatic NSCLC plus EGFR mutations.

Dacomitinib is an irreversible pan-HER TKI that has demonstrated preclinical activity as well as promising results in a phase II study of patients with EGFR mutations. In the ARCHER 1009 trial, patients who progressed after 1 or 2 prior chemotherapies were randomised to receive dacomitinib at 45 mg or erlotinib at 150 mg, both given orally each day. Each arm was placebo controlled.

The ARCHER results have been previously reported. Prof. Paz-Ares presented findings from a mutational analysis at ELCC. Archived tumour tissue was available for 47 patients in the dacomitinib arm and 44 patients in the erlotinib arm of ARCHER. Tests revealed activating mutations in exon 19 or 21 in 37 patients receiving dacomitinib and 39 patients receiving erlotinib. The PFS data were not mature and had a 56% event rate. Nevertheless, independent review for all EGFR mutants demonstrated patients receiving dacomitinib achieved median PFS of 11.1 months (95% CI 5.6, 21.9) compared to 10.0 months (95% CI 7.4, 16.6) for patients in the erlotinib arm; the HR was 0.935 (1-sided $p = 0.403$). The PFS per independent review of results from 76 patients with activating mutations in exon 19 or 21 receiving dacomitinib demonstrated median PFS of 14.6 (95% CI 7.6, NR) months compared to 9.6 (95% CI 7.3, 16.6) months for patients receiving erlotinib, unstratified HR 0.707 (1-sided $p = 0.136$). Similar PFS results were seen per investigator's assessment.

The OS results at <50% deaths were also immature; OS for patients with all mutations receiving dacomitinib was median 26.6 (95% CI 21.6, NR) months compared to 28 (95% CI 16.4, NR) months for patients receiving erlotinib, HR 0.976 (1-sided $p = 0.472$). The OS in the subgroup of patients with activating mutations was median 26.6 (95% CI 21.6, NR) months compared to 23.2 (95% CI 16.0, NR) months for patients receiving erlotinib, HR 0.798 (1-sided $p = 0.258$).

Toxicity profiles with each treatment were similar to the overall patient population, with the most commonly reported treatment-related adverse events being diarrhoea, paronychia, stomatitis, rash, dry skin, decreased appetite, and dermatitis acneiform. Adverse events that occurred more frequently with dacomitinib included diarrhoea (88.9%), paronychia (55.6%), stomatitis (52.8%), and decreased appetite (27.8%) whereas rash (66.7%), dermatitis acneiform (28.2%) and dermatitis acneiform cluster (30.8%) occurred more frequently with erlotinib. (Paz-Ares *et al.* Abstract 970) ARCHER 1009 was sponsored by Pfizer.

Practice point and future research opportunities

The phase III ARCHER trial directly compared two EGFR TKIs. Findings from an independent review of ARCHER data suggest that progression-free survival achieved with erlotinib could be improved upon by dacomitinib in patients with NSCLC. EGFR activating mutations seem to have a favourable impact with dacomitinib on progression-free survival. Further evaluation of dacomitinib versus erlotinib is planned in the ARCHER 1050 study.

Veliparib plus carboplatin and paclitaxel shows similar efficacy as carboplatin/paclitaxel in previously untreated metastatic or advanced NSCLC but demonstrates significant benefit in patients with squamous lung cancer

Julien Mazieres, CHU Toulouse, Hôpital de Larrey, Toulouse, France and colleagues conducted a randomised, double blind, phase II trial of veliparib, a potent, PARP inhibitor. Veliparib has been shown to be activated in response to DNA damage and facilitate DNA repair, and also has demonstrated an acceptable safety profile when combined with full dose carboplatin and

paclitaxel in phase I trials. This study comprised 158 patients with advanced or metastatic NSCLC; 49% has squamous NSCLC and 64% of patients were male. The majority of patients (69%) smoked within one-year of study entry; 105 patients were randomised to receive oral veliparib at 120 mg twice daily plus standard carboplatin/paclitaxel and 53 patients were randomised to placebo/carboplatin/paclitaxel; patients were stratified by histology and smoking history. The primary endpoint was PFS, with 80% power and $\alpha=0.05$, assuming log-rank HR of 0.51. All data analyses were performed at the 78th PFS event except OS, final as of November 6, 2014.

In the veliparib/carboplatin/paclitaxel arm, PFS in patients overall was 5.8 months, 6.1 months in patients with squamous histology and 4.3 months for patients with non-squamous NSCLC compared to 4.2, 4.1, and 5.0 months, respectively, for patients overall, patients with squamous, and patients with non-squamous NSCLC receiving placebo/ carboplatin/paclitaxel. The HRs for veliparib versus placebo in for patients overall, patients with squamous, and patients with non-squamous NSCLC were 0.71, 0.50, and 0.94, respectively. The OS in the veliparib cohort was 11.7, 10.3, and 12.8 months for patients overall, patients with squamous, and patients with non-squamous NSCLC compared to 9.1, 8.4, and 11 months for the respective subgroups of patients receiving placebo; HR 0.80, 0.73, and 0.90, respectively. The ORR was 31% with veliparib versus 28% with placebo and the DoR was 6.9 versus 3.3 months in the veliparib and placebo groups, respectively.

Preliminary veliparib pharmacokinetic data was available from 102 patients, which revealed that patients had comparable exposures to the agent regardless of smoking history. Adverse events occurring in $\geq 20\%$ of patients included alopecia (39% veliparib versus 42% placebo), anaemia (31% veliparib versus 42% placebo), neutropenia (36% veliparib versus 29% placebo), nausea (28% veliparib versus 25% placebo) and peripheral neuropathy, which occurred in 24% of veliparib patients versus 25% of patients in the placebo arm. Leukopenia occurred more often in patients receiving veliparib (11% veliparib versus 1% placebo). Adverse events of grades 3 or 4 were neutropenia, which was seen in 23% veliparib versus 19% placebo patients, and anaemia, which occurred in 10% of patients in each treatment arm. (Mazieres *et al.* Abstract 102PD)

Practice point and future research opportunities

Although the estimated hazard ratios for progression and death from NSCLC favoured veliparib/carboplatin/paclitaxel over placebo/carboplatin/paclitaxel, the results did not reach statistical significance. However, results from patients in the squamous histology subgroup support the initiation of a phase III trial to study veliparib in patients with squamous cell lung cancer.

Subgroup analysis shows variation in response to necitumumab added to gemcitabine/cisplatin in elderly patients: Results from SQUIRE, a randomised, multicentre, open-label, phase III study in patients with stage IV squamous NSCLC

Nicholas Thatcher, Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, reported findings from a subgroup analysis of data from elderly participants in the phase III randomised, open-label, SQUIRE trial of necitumumab added to gemcitabine-cisplatin. Patients in SQUIRE demonstrated prolonged OS in 545 patients treated with gemcitabine/cisplatin plus necitumumab, a fully human IgG1 anti-EGFR monoclonal antibody, over 548 patients receiving chemotherapy alone as first-line treatment. SQUIRE randomised 545 patients with pathologically proven stage IV squamous NSCLC to gemcitabine, cisplatin, and necitumumab and 548 similar patients to gemcitabine-cisplatin alone for up to 6 cycles. In the necitumumab arm, patients received necitumumab at 800 mg IV on days 1 and 8. Patients assigned to gemcitabine-cisplatin plus necitumumab showing no disease progression continued on necitumumab alone until progressive disease or intolerable toxicity.

At ELCC, findings were presented from an analysis of a subgroup of SQUIRE comprising 205 patients aged 77 or older compared to 888 patients less than 70 years. Excepting age, ECOG PS, and sex, the baseline characteristics between cohorts were well balanced. In the older cohort the median age was 73 years, patients were 88% male and ECOG PS was 0/1/2 in 27%, 58%, and 15% of patients, respectively; in the < 70 year cohort, the median age was 60 years, patients were 82% male and ECOG PS was 0/1/2 in 33%, 60%, and 7%, of patients, respectively

The older patients received slightly less exposure to necitumumab/gemcitabine/cisplatin and showed less clinical benefit from this treatment; median OS was 10 months versus 9.7 months in the necitumumab versus placebo groups, respectively, in the older cohort, hazard ratio (HR) for OS was 1.03 in this cohort for necitumumab/ gemcitabine/cisplatin versus chemotherapy alone ($p = 0.858$). Median OS was 11.7 versus 9.9 months with the respective treatments in the population <70 years, HR 0.81 ($p = 0.006$). PFS HRs for necitumumab versus gemcitabine-cisplatin were 0.82 ($p = 0.007$) for patients <70 years compared to HR 1.07 ($p=0.686$) for patients ≥ 70 years. In patients 70 years and older the PFS HR for the comparison between the necitumumab/ gemcitabine/cisplatin arm versus gemcitabine/cisplatin was HR 0.83 ($p = 0.615$).

Rates of treatment-emergent adverse events (TEAEs) with necitumumab/gemcitabine/cisplatin were similar between the older cohort and <70-year cohorts. However, in the older cohort 5.0% versus 2.0% of younger patients, respectively, reported febrile neutropenia of any grade. In addition, 11.9 older versus 8.7% of younger patients experienced any grade arterial thromboembolic events and 16.4% older versus 13.9% of younger patients experienced any grade venous thromboembolic events. (Thatcher *et al.* 103PD) The trial sponsor was Eli Lilly,

Practice point and future research opportunities

Patients with stage IV squamous non-small cell lung cancer in both age groups showed prolonged overall and progression-free survival outcomes with necitumumab/gemcitabine/cisplatin compared to gemcitabine/cisplatin. However these outcomes were less robust in patients aged 70 years and greater compared to younger patients less than 70 years, even though there was no evidence for an increased safety risk with necitumumab in the elderly cohort. Elderly patients are a unique population that need specifically designed clinical trials with adequate CGA; octogenarians, especially, should have specifically designed trials.

Monotherapy with third-generation agents represent a reasonable treatment choice for older patients and a platinum-based regimen with attenuated dose or weekly schedule could be considered for good PS elderly patients without significant comorbidities. Gefitinib is well-tolerated and has to be considered as first choice for EGFR-mutated patients.

Significantly improved progression-free survival with afatinib plus paclitaxel in patients with metastatic non–small-cell lung cancer who progressed on afatinib monotherapy following an initial response to gefitinib/erlotinib: Results from LUX-Lung 5

Martin Schuler, West German Cancer Center, University Duisburg-Essen, Essen, Germany, and colleagues conducted this phase III trial to prospectively assess whether continued irreversible ErbB-family blockade with afatinib (40 mg/day) and paclitaxel (80 mg/m² weekly) is superior to single agent chemotherapy (investigator choice) in patients with metastatic NSCLC. Patients experiencing disease progression after one or more lines of chemotherapy including erlotinib/gefitinib followed by afatinib after showing an initial benefit of 12 or more weeks were randomised 2:1; 134 patients were administered afatinib plus paclitaxel and 68 patients received single-agent chemotherapy.

Baseline characteristic were well matched between groups on the whole but there were several signals indicating that the afatinib/paclitaxel cohort had a high possibility of EGFR mutation; this cohort had fewer East Asian and more Caucasian patients, plus slightly fewer never smokers plus fewer smokers with <15 pack-years, who stopped more than one year prior to diagnosis.

The PFS, the primary endpoint, and ORR significantly improved with combination treatment; PFS was median 5.6 months with afatinib/paclitaxel compared to 2.8 months with chemotherapy; HR 0.60 (p = 0.0031) and the ORR was 32.1% versus 13.2% with afatinib/paclitaxel and chemotherapy, respectively (p = 0.005).

No significant difference in OS was observed between the two treatments. Median OS was 12.2 months with both afatinib/paclitaxel and chemotherapy (p = 0.994). The authors explained that OS may have reflected differences in post-progression treatment between arms since patients were on the 4th or greater line of therapy when randomised to afatinib/paclitaxel or

chemotherapy. Approximately 60% of patients had received one or more subsequent therapy post-progression; two additional lines of therapy were received by 15% of patients in the afatinib/paclitaxel arm compared to 36% of chemotherapy treated patients.

The incidence of treatment-related adverse events (AEs) was consistent with that previously reported for each agent. The most commonly reported AEs were diarrhoea, alopecia, and asthenia, which were reported by 53.8%, 32.6%, and 27.3% of patients in the afatinib/paclitaxel arms and by 6.7%, 15.0%, and 28.3% of chemotherapy patients, respectively. Global health status/QoL was maintained with afatinib despite longer exposure of 133 days versus 51 days with chemotherapy. (Schuler *et al.* Abstract 107PD)

Practice point and future research opportunities

Continued exposure to ErbB family blockade with afatinib in addition to paclitaxel resulted in superior progression-free survival and objective response rate versus chemotherapy alone in heavily pretreated patients with metastatic NSCLC that acquired resistance to erlotinib/gefitinib and experienced disease progression on afatinib monotherapy. Both significant (four or more lines) of prior therapies plus the possibility that the afatinib/paclitaxel cohort had a higher incidence of EGFR mutations may explain the similar overall survival response between treatment arms seen in this trial.

Benefit with second-line afatinib treatment of patients with advanced squamous cell carcinoma of the lung versus erlotinib following first-line platinum-based chemotherapy: Findings from LUX-Lung 8

Objective response and DCR by independent review were statistically better in patients with relapsed/refractory squamous cell carcinoma of the lung receiving afatinib than in patients treated with erlotinib, according to findings from the LUX-Lung 8, global, randomised, phase III study conducted by Glenwood Goss, Division of Medical Oncology, University of Ottawa, Ottawa, Canada and an international team of investigators. The LUX-Lung 8 study is a randomised, open-label, prospective phase III trial in patients with squamous cell carcinoma (SCC) of the lung who failed first-line platinum-based chemotherapy that directly compared afatinib with erlotinib, an EGFR inhibitor. Afatinib is an irreversible ErbB-family blocker that inhibits EGFR, HER2 and HER4.

Patients with stage IIIB/IV SCC were stratified by race as East Asian versus other to avert possible EGFR mutation imbalance, and randomised 1:1 to receive afatinib at 40 mg/day raised to 50 mg/day from cycle 2 onward for patients meeting adverse event (AE) criteria or erlotinib, given at the approved dose of 150 mg/day until disease progression. Recruitment of 795 patients took place from March 2012 until January 2014 and a primary analysis was planned based on 414 PFS, the trial's primary endpoint, events when 669 patients had been randomised; recruitment is ongoing and an OS, a key secondary endpoint, analysis is planned at 632 deaths whereupon PFS results will also be updated. An exploratory tumour genomic analysis is being performed. Baseline characteristics between 335 patients in the afatinib arm

and 334 patients in the erlotinib arm were well balanced; median age was 65 years, 85% of patients were male and 22% were eastern Asian.

The OR was 5% with afatinib versus 3% in erlotinib and DCR was 46% versus 37% with the respective treatments. Progressive disease occurred in 31% of afatinib patients versus 39% of erlotinib treated patients. Prolonged PFS was also seen with afatinib; median PFS in the afatinib arm was 2.4 compared to 1.9 months with erlotinib, hazard ratio (HR) 0.822; 95%CI 0.68, 1.00 ($p = 0.04$).

In the afatinib arm, 91% of patients reported an adverse event, 23% of patients had grade 3 AEs and 1% patient had a grade 4 AE. Rash/acne any grade was reported in 63% of patients and 6% of patients reported grade 3 rash/acne. Stomatitis any grade was seen in 27% of patients, grade 3 occurred in 3% of patients and fatigue any grade was reported by 13% of patients and grade 3 by 1% of patients; paronychia was seen in 11% of patients. In the erlotinib cohort, 80% of patients reported an AE and 15% of patients had a grade 3 AE. Rash/acne any grade was reported in 67% of patients and 9% of patients reported grade 3 rash/acne. Stomatitis any grade was seen in 8% of patients, and fatigue any grade was reported by 13% of patients, and grade 3 by 2% of patients; paronychia was seen in 4% of patients. (Goss *et al.* Abstract 108PD) Lux-Lung 8 was sponsored by Boehringer Ingelheim.

Practice point and future research opportunities

Objective response, disease control rate, prolonged progression-free survival, and improvements in patient reported outcomes all favoured afatinib over erlotinib in LUX-Lung 8, the largest prospective head to head comparison of afatinib to erlotinib in patients with relapsed/refractory squamous cell carcinoma of the lung. In term of targeted agents, afatinib may represent a better second-line treatment for this patient cohort than erlotinib.

Improved overall survival demonstrated with afatinib over chemotherapy in patients with NSCLC and EGFR L858R mutations across racial subgroups: Subgroup analyses of LUX-Lung 3 and LUX-Lung 6 data

Martin Schuler, West German Cancer Center, University Duisburg-Essen, Essen, Germany, and colleagues conducted a pre-planned subgroup analyses of OS according to race that compared Asian, non-Asian and Japanese patients participating in the phase III LUX-Lung 3 and 6 trials of first-line afatinib versus chemotherapy in patients with NSCLC and EGFR mutations. LUX-Lung 3 recruited 345 patients globally and LUX-Lung 6 recruited 364 Asian-only, excepting Japanese, patients. Both trials randomised patients 2:1 to receive either 40 mg/day of oral afatinib or up to 6 cycles of chemotherapy with cisplatin/pemetrexed and gemcitabine/cisplatin; patients were stratified by EGFR mutation into Deletion19, L858R mutation, or other mutation cohorts and by race into Asian or non-Asian cohorts.

In the overall cohort of patients with advanced NSCLC, OS with afatinib was 33.3 months versus 21.1 months with chemotherapy; hazard ratio (HR) 0.54 ($p = 0.0015$). Findings according to mutational status revealed OS in patients with activating EGFR mutations Deletion 19 or

L858R was median 31.6 months with afatinib versus 28.2 months with chemotherapy, HR 0.78 ($p = 0.109$) in LUX-Lung 3 and OS in LUX-Lung 6 was 23.6 versus 23.5 months with afatinib versus chemotherapy, respectively, HR 0.83 ($p = 0.176$) in the cohort with activating mutations.

Analysis of OS data by race in patients with EGFR activating mutation showed patients in the LUX-Lung Asian subgroup had OS of median 27.3 months with afatinib versus 24.7 months with chemotherapy; HR 0.82; 95% CI 0.66, 1.03 ($p = 0.083$). The non-Asian cohort showed median OS of 28.1 months with afatinib versus 20.7 months with chemotherapy, HR 0.68; 95% CI 0.39, 1.20 ($p = 0.179$) and the Japanese subgroup demonstrated median OS of 46.9 months with afatinib versus 35.0 months with chemotherapy, HR 0.57; 95% CI 0.29, 1.11 ($p = 0.097$).

Analysis of OS data specifically for patients harbouring the EGFR Deletion19 mutation in the non-Asian subgroup showed OS in 30 patients receiving afatinib was median 33.6 versus 20.0 months in 16 patients receiving chemotherapy, HR 0.45 ($p = 0.031$). In Asian patients, median OS was 31.7 versus 21.1 months in 206 patients receiving afatinib and 103 patients receiving chemotherapy, respectively, HR 0.61 ($p = 0.001$). In the Japanese cohort, median OS was 46.9 versus 31.5 months in 23 patients receiving afatinib and 16 patients receiving chemotherapy, respectively, HR 0.34 ($p = 0.018$). (Schuler *et al.* Abstract 109PD) The LUX-Lung trials were sponsored by Boehringer Ingelheim.

Practice point and future research opportunities

A preplanned subgroup analysis demonstrated that significant improvement in overall survival was achieved with first-line afatinib versus chemotherapy in patients with advanced NSCLC and activating mutations that was especially prolonged in Japanese patients. Afatinib improved overall survival over chemotherapy in patients across all racial subgroups with EGFR Deletion19 mutation, with the strongest effect again seen with Japanese ethnicity. However, the non-Asian and Japanese cohorts were quite small, so results should also be obtained from larger populations.

Metastasis in a single organ associates with improved overall survival in patients with stage IV non-small cell lung cancer

Lisa Hendriks, Maastricht University Medical Center, Maastricht, Netherlands, and colleagues conducted an analysis of risk factors, including age, histology, M-status (TNM7 M1a versus M1b and TNM6 M1), gender, single versus multiple organ metastases, the organ affected, and the local disease status to determine their prognostic impact on OS in stage IV NSCLC. The investigators evaluated data from 11,094 patients with histologically confirmed stage IV NSCLC diagnosed over a six-year period beginning 01 January 2006 and recorded in the Netherlands Cancer Registry. Patients were 60% male with a mean age of 65 years and 73% had adenocarcinoma. Patients were also assigned to two subgroups for separate evaluation: those staged by ¹⁸FDG-PET and patients currently receiving anticancer treatment.

In 5676, and 3280, 2138 patients having one, two or three or more organs with metastasis, median OS was 10.4, 7.3 and 5.7 months, respectively ($p < 0.001$). In the subgroup of 1517

patients with disease staged by ¹⁸FDG-PET, median overall OS for 1, 2, and ≥3 metastatic organs was 8.6, 5.7 and 3.8 months, respectively ($p < 0.001$). Upon multivariate analysis, the number of organs involved associated significantly with OS; the hazard ratio (HR) for 2 involved organs versus 1 metastatic organ was 1.4 ($p < 0.001$), and the HR for ≥ 3 versus 1 organ was 1.9 ($p < 0.001$). In this subgroup, median OS for high versus low TN-status was 9.9 months versus 13.7 months, HR 1.5 ($p < 0.001$).

NSCLC patients with increasing severity of comorbidity were less likely to undergo surgical resection than patients with no recorded comorbidity [case-mix adjusted OR 0.58 (95% CI 0.46-0.74) for Charleston Cancer Score (CCS) 3+ versus CCS 0, $\chi^2=33.12$, $p\text{-trend}<0.0$. Among the resected NSCLC patients, increasing comorbidity score was associated with higher death; HR 1.45 (95%CI 1.07-1.98) for CCS 3+ versus CCS0, $\chi^2=20.04$, ($p\text{-trend} < 0.001$). No association was seen between mortality and high CCS in the first 30 days post-surgery or in the 30 to 365 days post-surgery; however, comorbidity associated with survival in the >365 days post-surgery period [case-mix adjusted HR 1.67; 95% CI 1.04, 2.69 for CCS 3+ versus CCS 0, $\chi^2=12.51$ ($p\text{-trend}<0.001$)] .

In the analysis of patients with one metastatic organ only, intrathoracic metastasis (current M1a) and extrathoracic lymph node (ET-LN) metastasis were associated with superior OS; pulmonary metastasis HR 0.6, pleural metastasis HR 0.8 and ET-LN HR 0.8. Separate analyses for TNM6 and TNM7 yielded comparable findings. (Hendriks *et al.* 110PD)

Practice point and future research opportunities

Patients with stage IV NSCLC have a more favourable prognosis for overall survival when metastasis involves a single organ, especially in combination with low TN status. The prognosis for overall survival becomes poorer as more organs are involved and the TN status is higher, and these factors remain constant across subgroups of patients currently undergoing treatment and patients with disease staged by ¹⁸FDG-PET. However, in patients with distant metastasis (current M1b) no organ consistently associated with a superior OS, excepting extrathoracic lymph node metastasis. This analysis would be strengthened by knowing whether disease was synchronous or metachronous and with overall survival was stratified in single organ M1 such as adrenal versus brain.

Among resected NSCLC patients, comorbidity is an independent prognostic factor for longer term survival; among all other lung cancer patients not undergoing surgical resection, the effect of comorbidity is largely explained by performance status.

Ceritinib shows intracranial efficacy and disease control in patients with ALK-rearranged non-small cell lung cancer and brain metastases: Results from a subgroup analysis of ASCEND-1

Lead poster author Dong-Wan Kim, Seoul National University Hospital, Seoul, Korea, reported results from a trial of ceritinib in patients with rearranged ALK NSCLC experiencing brain metastases as disease progression, including those receiving prior crizotinib, Ceritinib is a novel

second-generation oral ALK inhibitor that has shown 20-fold greater potency than crizotinib in enzymatic assays, demonstrated blood-brain barrier penetration in preclinical studies, and showed intracranial activity in the phase I ASCEND-1 study. Of the 246 patients with ALK-positive NSCLC participating in ASCEND-1, 83 were naive to ALK inhibitors and 163 had been pre-treated with ALK inhibitors. The response rate for ALK inhibitor-naïve and pre-treated patients was 72.3% and 56.4%, respectively. The PFS in the respective groups was 18.4 months in ALK inhibitor-naïve and 6.9 months in ALK-inhibitor pre-treated patients.

At ELCC, Dr. Kim presented further efficacy and safety data from a subgroup of patients in ASCEND-1 with disease progression to the brain. ASCEND-1 included 94 patients with clinically/neurologically stable brain metastases who received ceritinib at 750 mg/day; median ceritinib treatment exposure was 49.6 weeks (range: 7.9 to 83.0) and 40.6 weeks (range: 0.4 to 95.1) in ALK inhibitor-naïve and ALK inhibitor-pre-treated patients, respectively. All patients had measurable (by RECIST 1.1) or non-measurable brain metastases plus MRI/CT scans taken at baseline and at data cut-off that were retrospectively analysed; the median patient age was 52 years, and the ECOG PS was ≤1 in 86.2% of patients.

The majority of patients achieved intracranial disease control with ceritinib; the intracranial disease control rate, defined as complete and partial response plus stable disease, was 78.9% (95% CI 54.4, 93.9) in 19 ALK inhibitor-naïve patients and 65.3% (95% CI 53.5, 76.0) in 75 ALK inhibitor-pre-treated patients. Further analysis revealed that 6 of the 11 patients with measurable brain metastases not receiving prior radiotherapy achieved a partial response. The median time to tumour response was 6.1 weeks in all 22 patients with measurable baseline brain metastases. The incidence of adverse events of all grades was similar between the overall patients and patients with brain metastases; the most commonly reported adverse events in patients overall and in the subset, respectively, were diarrhoea (86.6% versus 81.9%), nausea (83.3% versus 86.2%), and vomiting (61.0% versus 66.0%). (Kim *et al.* 111P) The ASCEND-1 trial was sponsored by Novartis.

Practice point and future research opportunities

Ceritinib demonstrated activity and safety in patients with ALK-positive NSCLC and brain metastases regardless of whether or not they were previously treated with an ALK inhibitor.

Improved progression-free survival with third-line anlotinib in patients with refractory advanced non-small cell lung cancer

Lead investigator Baohui Han, Shanghai Chest Hospital, Shanghai, China, presented efficacy and safety results demonstrating that anlotinib prolonged PFS over placebo in patients with refractory advanced NSCLC. His team conducted a randomised, double-blind, placebo-controlled trial of anlotinib given as third-line therapy with platinum-based chemotherapy. All patients had histological or cytological confirmed, metastatic or recurrent advanced non-squamous NSCLC with an ECOG performance status of 0–1; 60 patients were treated with anlotinib at 12 mg/day, *per os* on days 1 through 14 every 3-weeks and 57 received placebo until progression, unacceptable toxicity, withdrawal of patient consent or death occurred.

The PFS was more than tripled with anlotinib; PFS was 4.83 months with anlotinib compared to 1.23 months with placebo; hazard ratio (HR) 0.32 ($p < 0.0001$). The overall response rate was 13.3% with anlotinib compared to 0% with placebo ($p < 0.006$) and the disease control rate was 93.3% with anlotinib and 30% with placebo ($p < 0.0001$). The OS data are not yet mature. Adverse events grades I/II were more frequently reported with anlotinib and grade III/IV treatment-related adverse events increased 16.4% with anlotinib over placebo. No grade 5 toxicities were recorded. (Han *et al.* Abstract 113P)

Practice point and future research opportunities

Chinese patients with refractory advanced non-small cell lung cancer showed statistically significant clinical benefit from anlotinib plus third-line platinum-based chemotherapy without raising serious safety concerns.

Promising phase Ib study results with demcizumab plus pemetrexed and carboplatin as first-line treatment for patients with non-squamous NSCLC

Jakob Dupont, OncoMed Pharmaceuticals, Redwood City, USA, presented results from a small phase Ib study that aimed to determine the maximum tolerated dose, safety, efficacy, immunogenicity, and pharmacokinetics of demcizumab, a humanized IgG₂ antibody that inhibits delta-like ligand 4 (DLL4) a molecule in the NOTCH signalling pathway. Demcizumab had previously demonstrated activity in patient-derived tumour xenograft models, where demcizumab inhibited tumour growth, decreased the number of cancer stem cell and showed anti-angiogenic effects through the dysfunctional sprouting of new vessels. The investigators also aimed to identify biomarkers of Notch signalling following treatment.

Decizumab was administered to 39 patients with non-squamous NSCLC; treatment arms 1 to 4 included 6 patients who received 2.5 mg/kg and 20 patients that received 5 mg/kg of demcizumab plus pemetrexed and carboplatin every three weeks for six cycles followed by maintenance with demcizumab. In cohort 5, six patients received 7.5 mg/kg of demcizumab and, in cohort 6, seven patients received 5 mg/kg of truncated demcizumab plus pemetrexed and carboplatin every three weeks for six cycles followed by maintenance with demcizumab.

Thirty-three patients were evaluable; of these 1(3%) patient achieved a complete response by RECIST, 15 (45%) patients showed a partial response, and stable disease (SD) was achieved by 13 (39%) patients, yielding an overall clinical benefit rate of 88%. In the cohorts treated with 5 and 7.5 mg/kg of demcizumab, 8 patients remained progression free for more than 300 days and 6 patients remained disease free on days 408+, 448+, 456+, 546+, 677+ 680+, with no current therapy and 2 patients receiving no current therapy progressed after 314 and 850 days.

Demcizumab treatment was limited to 63 days in arms 5 and 6 due to increased B-type natriuretic peptide (BNP). Elevated BNP occurred in 26% of patients and, since increased BNP is an early indicator of cardiac effects of demcizumab, patients with mildly elevated BNP values received cardioprotective therapy with an ACE inhibitor or carvedilol, and treatment was stopped in patients receiving the higher doses of BNP. In arms 1 to 4 wherein patients received

demcizumab at 5mg/kg, two patients developed reversible pulmonary hypertension with heart failure on treatment days 167 and 183. Six patients went off study for reasons other than disease progression. The most frequent adverse events (AEs) that were reported for more than 20% of patients were nausea, reported for 51% of patients, fatigue and hypertension, each occurring in 46% of patients, vomiting in 31%, oedema and neutropenia, each reported by 26% of patients, and anaemia, which was reported in 21% of patients. (Dupont *et al.* Abstract 114P)

Practice point and future research opportunities

First-line combination therapy of pemetrexed and carboplatin plus demcizumab showed promising results, including response rate and progression-free survival in patients with non-squamous NSCLC. However, the optimal dose of demcizumab has not been determined and, although the safety profile was generally in line with that of pemetrexed and carboplatin, elevated BNP levels requiring treatment were reported.

Cabozantinib shows benefit in patients with KIF5B and CCDC6 RET mutated lung cancer

Michal Sarfaty, Rabin Medical Center Davidoff Cancer Centre, Beilinson Campus, Petach Tikva, Israel, presented a genetic analysis of patients with lung adenocarcinomas, intending to contribute to the natural history and clinical management of patients with RET mutated lung cancer. Data were analysed from a series of 4 male and 4 female patients with lung adenocarcinoma that were participating in a multicentre, retrospective study. The report comprised 8 lung cancer patients with RET fusion and a mean age of 51 years (range: 28 to 72); 50% of patients were light smokers and 50% of patients were never-smokers. The KIF5B-RET variant was identified in 5 patients and 3 had the CCDC6-RET. The KIF5B variant was confirmed in 4 of the 5 patients with hyper-acute presentation and/or recurrence.

A female patient with KIF5B-RET received cabozantinib and achieved a complete response according to RECIST criteria that lasted for 8 months. This patient also presented with bilateral miliary lung metastasis and showed early involvement of the liver, ovaries, intestine, and bone. According to the authors, this is the first report of a complete response to cabozantinib for this indication. One patient with CCDC6-RET mutation had a response lasting 8 months to cisplatin/pemetrexed/bevacizumab. (Sarfaty *et al.* Abstract 115P)

Practice point and future research opportunities

Patients with lung adenocarcinoma plus RET-fusion may have an abrupt and acute presentation and may also demonstrate a KIF5B subtype. Cabozantinib provided clinical benefit in one patient and warrants further evaluation.

Icotinib shows promise as first-line treatment for elderly patients with EGFR 19 or 21 mutation in advanced NSCLC

Baohui Han, and colleagues from the Shanghai Chest Hospital, Shanghai, China presented findings from a phase IV, open-label, single-arm study of first-line icotinib in elderly patients with NSCLC and specific EGFR mutations. Icotinib is an oral EGFR tyrosine kinase inhibitor that had previously demonstrated antitumour activity and favourable toxicity in the ICOGEN trial. This trial evaluated icotinib in 35 chemotherapy-naïve patients, 17 female and 18 male patients, with a median age of 76 years (range: 70 to 82 years) that had stage IIIB (n=9) or IV (n=26) NSCLC; 30 patients had adenocarcinoma, 5 had non-adenocarcinoma and 22 (62.8%) were never smokers. All patients harboured EGFR mutation; 16 patients had exon 19 deletions and 19 had L858R mutations.

Icotinib was administered at 125 mg three times daily until disease progression or unacceptable toxicity.

Median PFS, the primary endpoint, was 19.5 months; (95% CI 12.3, NR) and median OS, a secondary endpoint, had not yet been reached. The overall response rate was 62.9%. No patients achieved a complete response, 22 patients had partial response, 12 patients showed stable disease and just one patient experienced disease progression, yielding a disease control rate of 97.1%. The most commonly reported adverse events were rash, reported for 65.7% of patients, diarrhoea in 45.7%, and anorexia, which was reported by 14.39% of patients; one patient experienced a grade 3 skin rash. No lung toxicities were reported. (Han *et al.* Abstract 122P)

Practice point and future research opportunities

First-line icotinib provided clinical benefit in elderly patients with EGFR exon 19 deletions and L858R mutations who demonstrated a 97.1% disease control rate with first-line icotinib.

MESOTHELIOMA

Over-expression of PD-L1 in pleural mesotheliomas

Andreas Voss, Caris Life Sciences, Basel, Switzerland, noted that the prognosis for patients with pleural malignant mesothelioma (PLMM) remains poor, especially at progression after initial surgical treatment. Although pemetrexed and platinum combination chemotherapy are the current standard therapy for unresectable disease, new immune-modulation therapies may offer additional benefit for a selected group of patients, leading the investigators to investigate the expression of PD-L1 and PD-1 as potential biomarkers in mesotheliomas.

This study comprised 21 patients; samples from 9 males and 5 females aged from 41 to 80 years with PLMM and 2 males and 5 females aged from 40 to 86 years with peritoneal malignant mesotheliomas (PEMM) were analysed by immunohistochemistry (IHC), in-situ hybridization (ISH) and molecular next generation sequencing (NGS) to identify biomarkers of targeted therapies activity

PD-L1 was overexpressed, defined as 2+ in $\geq 5\%$ of cells, was identified in 10 of 14 PLMM specimens compared to PD-L1 overexpression in just 2 of 7 PEMM cases. Both tumour types showed infiltration with PD-1 positive lymphocytes, a characteristic of malignant mesotheliomas. Over-expression of PD-L1 on mesothelioma cells and PD-1 on tumour infiltrating lymphocytes was seen in 9 cases of PLMM. Four of the PD-L1 positive PLMM had concomitant low expression of thymidylate synthase. Additionally, c-Met was over-expressed in both pleural and peritoneal mesotheliomas; 4 of 13 PLMM and 3 of 7 PEMM were without gene amplification. No activating mutations were found in several tyrosine kinase genes, including HER2, EGFR and c-MET. One activating mutation in KRAS (G12V) was observed in one PLMM case. (Voss *et al.* Abstract 157P)

Practice point and future research opportunities

Malignant mesotheliomas of pleura frequently (>70%) overexpress PD-L1, which makes these tumours potential candidates for the targeted immune therapies aimed at inhibition of PD-1/PD-L1 interaction. Combination of immune therapies with conventional pemetrexed chemotherapy may be plausible in a significant portion of PD-L1 positive patients, as suggested by a concurrent low expression of thymidylate synthase.

Standard chemotherapy does not alter expression of genes necessary for check-point blockade may in patients with malignant pleural mesothelioma

Alessandra Curioni-Fontecedro presented findings on behalf of colleagues at the University Hospital Zurich, Zurich, Switzerland, from a study that assessed whether immunotherapy could be effective in treating patients with mesothelioma, as preclinical data suggest. For this evaluation, the investigators determined whether molecules such as the programmed death receptor 1 (PD-1), its ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC), CD275 (ICOS-L) and CD276 (B7-H3) are expressed on mesothelioma tumours and whether expression is downregulated by

chemotherapy, which would alter the utility of immunotherapy. The investigators compared expression of HLA-I and II, PD-L1, ICOS-L and B7-H3 using a Tissue Microarray (TMA) in 88 tumour samples from untreated mesothelioma patients to the expression of these molecules in whole tumour samples from 10 patients taken both before and after chemotherapy; findings were confirmed by the expression of these molecules on mesothelioma cell lines following treatment with combination cisplatin/pemetrexed or gemcitabine.

By TMA, HLA-I was expressed in 79 (90%) of 88 tumour samples from patients with untreated mesothelioma; in 88 samples, HLA-II was expressed in 14 (16%) samples. These samples were 90% positive for ICOS-L and 69% of cases were positive for B7-H3. In whole tumour, levels of PD-L1 and FoxP3 increased in the tumour and stroma following treatment; no down-regulation of any of these molecules was observed when comparing matched whole tumour sections before and after treatment in patients receiving cisplatin/pemetrexed. This result was also confirmed by data obtained using mesothelioma cell lines before and after treatment with chemotherapeutics. (Curioni-Fontecedro *et al.* Abstract 155O)

Practice point and future research opportunities

Findings from an analysis of tumour samples performed before and after chemotherapy showed molecules important for checkpoint blockade with immunotherapy are expressed on tumours from mesothelioma patients and this expression is not affected by standard chemotherapy. These results suggest that immunotherapy may offer a needed, rational, new treatment option for patients with mesothelioma that are either chemotherapy naive or have received chemotherapy. Clinical trial evaluation of the potential clinical benefit of immunotherapeutics in patients with mesothelioma is warranted.

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ELCC European Lung Cancer Conference, 13-16 April 2016, Geneva, Switzerland.

Affiliation and Disclosure

Affiliation

Dr Svetlana Jezdic, ESMO Head Office.

Disclosure

No conflicts of interest to disclose.

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