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Congress Report ECC 2015

A GLOBAL CONGRESS DIGEST ON NSCLC

Report from the 18th ECCO- 40th ESMO European Cancer Congress, Vienna 25th–29th September 2015

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Lecture Board for this issue: Maximilian Hochmair, MD; Helmut Prosch, MD; Martin Filipits, MD

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Preface

Dear Colleagues,

Oncologists are currently witnessing rapid diagnostic and therapeutic advances in their field. These advances require that physicians are up-to-date regarding the ever-changing standards of care. With the present publication, we hope to contribute to this goal, by summarising recent findings in the diagnosis and treatment of lung cancer, as presented at the European Cancer Congress (ECC) that took place in Vienna, from 25th–29th September, 2015.

Innovations for patients with advanced non–small-cell lung cancer are of particular interest due to their poor prognosis. Targeted agents have already been shown to improve survival outcomes in this setting. The latest analyses shed light on their effects on other important endpoints, such as quality of life, and define the benefits of new drugs in difficult-to-treat subgroups. Refined molecular testing techniques have become available, although their wide-spread implementation in clinical practice has yet to be improved.

Significant therapeutic advances were also shown for the immune checkpoint inhibitors nivolumab and pembrolizumab, while new representatives of this drug class, such as atezolizumab, are well on their way. Nivolumab also excelled in the treatment of patients with small-cell lung cancer. However, the patient selection through predictive biomarkers still needs further research with regard to these novel immunotherapeutics.

Early-stage and locally advanced non–small-cell lung cancer deserves attention as well, in particular with regard to improving long-term outcomes. For patients with adenocarcinoma, the selection of patients for adjuvant chemotherapy might be improved by use of the IASL/ATS/ERS classification in the future. Finally, sublobar resection was shown to be feasible in stage IA tumours according to HRCT and maximum standardized uptake values on FDG-PET/CT.

Robert Pirker, MD, Medical University of Vienna, Vienna, Austria

News on targeted agents in the advanced setting

Afatinib in squamous-cell carcinoma: update of LUX-Lung 8

Squamous-cell carcinoma of the lung represents approximately 30 % of non–small-cell lung cancer (NSCLC) cases. Until 2015, docetaxel and erlotinib were the only approved second-line treatment options in these patients. Typically, squamous-cell carcinoma of the lung has a high burden of somatic mutations and genomic alterations. Overexpression and dysregulation of EGFR, FGFR1, PI3K and their downstream pathways are implicated in the pathogenesis, providing a rationale for the use of ErbB inhibitors in this setting of major medical need.

The global, open-label, randomised, phase III LUX-Lung 8 trial compared the irreversible ErbB family blocker afatinib with the reversible EGFR tyrosine kinase inhibitor (TKI) erlotinib in a total of 795 patients with squamous-cell carcinoma of the lung after failure of first-line platinum-based chemotherapy. Compared to erlotinib, afatinib significantly improved progression-free survival (PFS; median 2.4 vs. 1.9 months; HR, 0.82, 95 % CI 0.68-1.00, p = 0.0427) and overall survival (OS; median 7.9 vs. 6.8 months; HR, 0.81, 95 % CI 0.69-0.95; p = 0.0077; Figure 1) [1]. The OS effect of afatinib was consistent across subgroups.

At the ECC, the updated PFS results and exploratory genetic analyses using next-generation sequencing of select tumour samples were reported [2]. The PFS results significantly favoured afatinib (2.6 vs. 1.9 months; HR, 0.81; p = 0.0103). Furthermore, there was a significant improvement in disease control rate (DCR; 50.5 % vs. 39.5 %; p = 0.002). More patients in the afatinib group had an objective response (5.5 % vs. 2.8 %), and median duration of response was longer than in the erlotinib arm (7.3 vs. 3.7 months). Adverse events (AEs) occurred in both arms at similar rates, which also applied to grade ≥ 3 AEs.

No biomarkers for the selection of patients for treatment with afatinib were identified. According to the biomarker analyses, the prevalence of *EGFR* genomic aberrations was consistent with prior reports in patients with squamous-cell carcinoma, and no predictive associations between genetic alterations and OS or PFS were observed. Assessment of EGFR immunohistochemistry and blood-based markers is ongoing, as well as further bioinformatics analysis of next-generation sequencing.

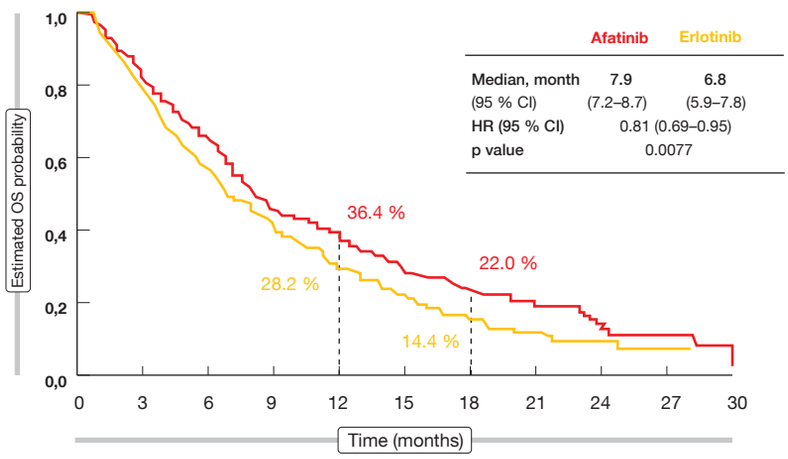

Figure 1: Overall survival with afatinib versus erlotinib in LUX-Lung 8

Quality of life and other outcomes

The outcome improvements obtained in LUX-Lung 8 were accompanied by similar changes in patient-reported outcomes [3]. Prespecified analyses using the European Organisation for Research and Treatment of Cancer (EORTC) core quality-of-life questionnaire (QLQ-C30) and its lung-cancer-specific module (QLQ-LC13) showed significantly higher proportions of patients reporting improved global health status/ quality of life and cough with afatinib than with erlotinib. For dyspnoea and pain, a non-significant advantage of afatinib compared with erlotinib was observed. Afatinib significantly delayed time to deterioration (TTD) of dyspnoea compared to erlotinib, and there was a trend towards delayed TTD of cough. Changes in mean scores over time significantly favoured afatinib over erlotinib for cough (p = 0.0091), dyspnoea (p = 0.0024), and pain (p = 0.0384).

A diarrhoea substudy (n = 63) analysed the time course and severity of diarrhoea using patient diaries at selected centres. In this substudy, the overall incidence of all-grade diarrhoea was similar to that reported in the overall trial population (86.1 % with afatinib, 51. 8 % with erlotinib). Nineteen percent (7 out of 36) of afatinib-treated patients reported grade ≥ 3 diarrhoea, with a mean duration of 3 days. No patient discontinued study treatment due to this AE.

Overall, these analyses confirm the clinical relevance of the improvements observed for PFS, OS and tumour response with afatinib in LUX-Lung 8. The researchers concluded that afatinib should be considered the TKI of choice for second-line treatment of squamous-cell carcinoma of the lung.

Assessment of nintedanib in squamous-cell carcinoma

Nintedanib is an oral triple angiokinase inhibitor that targets factors of three major proangiogenic pathways. Based on the results of the randomised, placebo-controlled, phase III LUME-Lung 1 study [4], nintedanib has been approved in combination with docetaxel in the Euro-

pean Union and in Russia for the treatment of patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology after first-line chemotherapy. Investigations in other histological subgroups of NSCLC patients are ongoing. As an example, a multicentre, phase I, dose-escalating study analysing nintedanib in combination with standard doses of gemcitabine and cisplatin for up to 6 cycles shows promising activity for the first-line treatment of patients with advanced squamous-cell carcinoma [5]. Disease control was achieved in 81.3 %, and the 6-month OS rate was 69 %.

Continuous treatment with nintedanib 200 mg twice daily together with cisplatin/ gemcitabine had a manageable safety profile. Nausea, asthenia, decreased appetite, and constipation were the most frequent AEs. The pharmacokinetic profile of nintedanib and its main metabolites in combination with chemotherapy were comparable to previous nintedanib monotherapy trials. There were no relevant interactions between gemcitabine/ cisplatin and nintedanib at the treatment schedule used. Further research is warranted to determine whether antiangiogenic therapy is an effective treatment option in patients with squamous-cell NSCLC.

Reductions in tumour burden in LUME-Lung 1

An analysis of the LUME-Lung 1 study investigated the impact of treatment with nintedanib plus docetaxel on tumour growth over time [6]. Tumour burden has been shown to be associated with clinical outcomes in NSCLC; decreases in tumour burden and slowing of tumour growth is an important outcome for patients. Patients with poor prognosis in LUME-Lung 1 were included in this analysis, as well as patients with adenocarcinoma who had progressed within 9 months after start of first-line therapy, patients who had progressive disease as best response to first-line therapy, and all of the patients with squamous-cell carcinoma histology.

Baseline tumour burden was greatest in adenocarcinoma patients with progressive disease as best response to first-line therapy, followed by patients who progressed within 9 months of starting first-line therapy. The combination of nintedanib and docetaxel significantly decreased tumour burden and decelerated tumour growth over time compared to placebo plus docetaxel in all patients with adenocarcinoma histology. Improvements in tumour burden were greatest in those with larger baseline tumour burden. The two groups of patients with the poorest prognosis, as mentioned above, showed similar results (Figure 2).

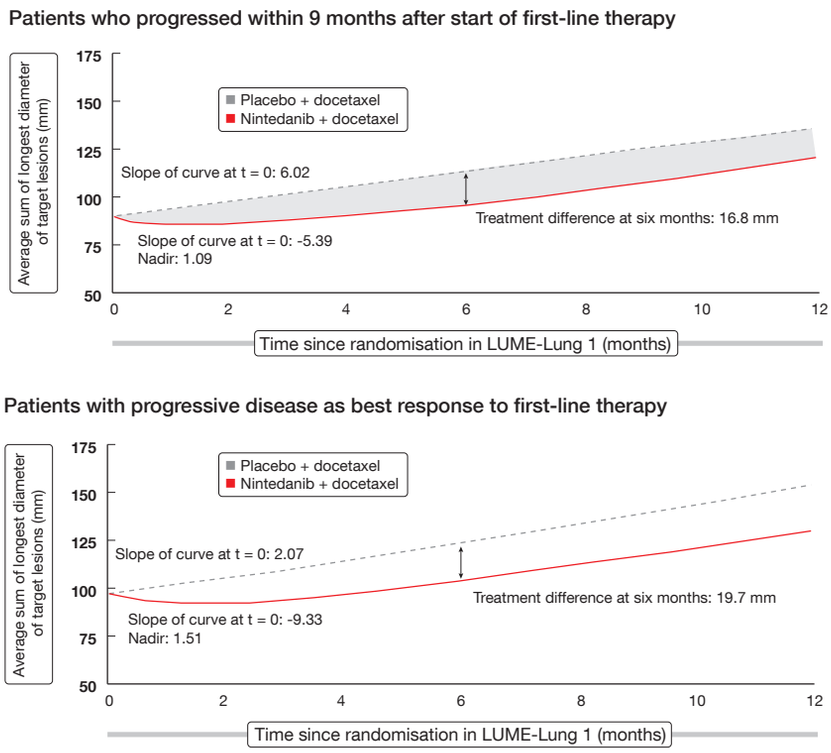

Figure 2: Tumour growth over time in patients with poor prognosis in LUME-Lung 1

T790M resistance mutation: erlotinib plus bevacizumab

Activating *EGFR* mutations are found in approximately 15 % of all NSCLC tumours, which provides the basis for EGFR TKI therapy, either as a first-line or later-line treatment option after chemotherapy. However, approximately 60 % of patients who receive EGFR TKI treatment develop the acquired resistance mutation T790M. Identifying strategies to overcome this therapeutic obstacle has become an important area of research.

The open-label, multicentre, phase II ETOP 2-11 BELIEF trial investigated the combination of erlotinib and bevacizumab in patients with advanced non-squamous NSCLC with activating *EGFR* mutations with and without T790M [7]. The rationale for this trial was the hypothesis that combined VEGFR/ EGFR pathway blockade might be beneficial in the presence of T790M. Patients with activating *EGFR* mutations were treated with erlotinib 150 mg and bevacizumab 15 mg/kg every 3 weeks until progression. Pre-treatment T790M mutations were identified centrally. Overall, 109 patients were enrolled. Substudy 1 included patients with T790M (n = 37), whereas those without T790M were assessed in substudy 2 (n = 72).

The combination of erlotinib and bevacizumab resulted in an overall 1-year PFS rate of 56.7 % and median PFS of 13.8 months. In patients with documented T790M mutation, the 1-year PFS rate was 72.4 % and the median PFS was 16.0 months; thus, the predefined endpoint for success was reached. Patients without T790M had a 1-year PFS rate of 49.4 % and median PFS of 10.5 months. Those with T790M at baseline fared better across subgroups. With one exception, all patients experienced tumour shrinkage. No unexpected toxicities were identified.

Further investigations using multiple orthogonal methods including digital polymerase chain reaction and multi-

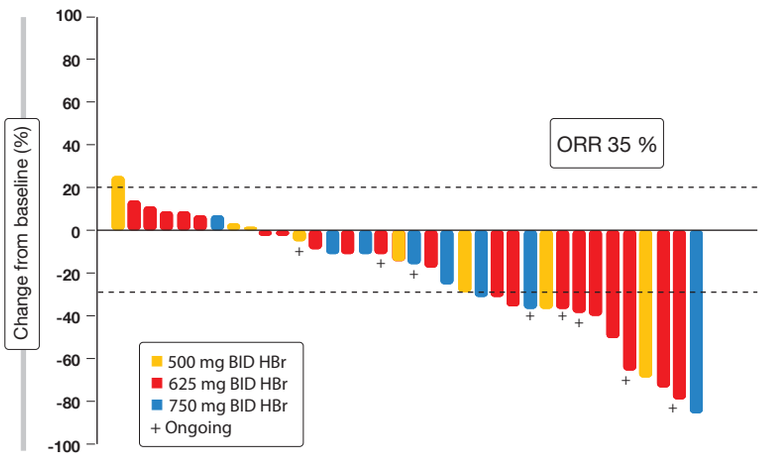

Figure 3: Waterfall plot of best RECIST response for target lesions obtained with rociletinib in T790M-negative patients

plex next-generation sequencing are ongoing.

Rociletinib in T790M-negative patients

There is an unmet medical need for new therapies that are active in both T790M-positive and T790M wild-type NSCLC patients who progressed after EGFR TKI treatment. Rociletinib, a novel, oral, selective covalent EGFR TKI, was developed to address key activating mutations together with the T790M mutation.

TIGER-X was a phase I/II study that investigated rociletinib in previously treated, *EGFR*-mutant patients with advanced or recurrent NSCLC and both T790M-positive (n = 111) and T790M-negative (n = 482) mutation status. Phase 1 of the trial was conducted for dose-escalation, while in phase 2, expansion cohorts were treated. One cohort consisted of second-line patients with disease progression upon one immediate prior TKI, and the other comprised patients beyond second line who had experienced progression upon at least two TKIs or chemotherapy. Treatment was conducted with rociletinib 500 mg, 625 mg or 750 mg, twice daily (BID).

The analysis presented at the ECC focussed on updated results in centrally confirmed tissue T790M-negative patients [8]. Overall response rate (ORR) was 35 % in this population (Figure 3). Disease control occurred in 65 %. A comparison of available tissue-based testing assays (Therascreen® and Cobas®) yielded highly concordant results. Plasma T790M testing revealed an ORR of 45 % and a DCR of 83 % in patients with negative mutation status. The investigators stated that plasma tests may be more representative, especially with extra-thoracic spread. However, the greater rate of false negatives has to be taken into account. The most common treatment-related AEs were similar to those observed in the general TIGER-X patient population.

It is possible that the efficacy of rociletinib in T790M-negative patients is driven in part by clonal heterogeneity, as not all cells express T790M, or by the inhibitory effect on insulin-like growth factor 1 receptor (IGF-1R) and insulin receptor (IR) kinases. IGF-1R/ IR might drive resistance to initial EGFR inhibitor therapy. TKI retreatment may not be a likely explanation, as the majority of patients had a recent history of progression on EGFR TKI therapy. In view of these results, the clinical profile of rociletinib in T790M-negative NSCLC patients continues to be encouraging. The efficacy of rociletinib in this population is currently being evaluated in the TIGER-2 and TIGER-3 clinical studies.

Activity of rociletinib against the background of CNS disease

Central nervous system (CNS) metastases occur in up to 50 % of advanced NSCLC cases. In EGFR-mutant patients treated with first-generation EGFR TKIs, the 2-year CNS progression rate is 21 %, and 40 % among those with a prior history of CNS disease.

Patients with asymptomatic treated CNS metastases were allowed to participate in the TIGER-X study. A T790M-positive biopsy was required at the time of study entry in phase 2 of the trial. In this phase, a total of 41 % of patients with a history of CNS disease were treated. This factor did not appear to affect response rates, as the ORRs among patients without and with a history of CNS metastases were 58 % and 45 %, respectively [9]. DCRs were 92 % and 75 %, respectively. Also, the CNS radiation rate on study was assessed on the assumption that CNS radiation and post-progression TKI therapy can be used as a surrogate for CNS progression on rociletinib. Based on these parameters, it was estimated that 15 % of progressing patients might have CNS progression on rociletinib, which is lower than available historical data on erlotinib.

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Rociletinib might provide ongoing extracranial disease control in patients who received CNS radiation due to progressive disease.

The study treatment was generally well tolerated, with 2.5 % of patients discontinuing the trial due to treatment-related AEs. Hyperglycaemia and diarrhoea were the most frequent toxicities. Hyperglycaemia was the only grade ≥ 3 AE observed in >10 % of patients; it occurred in 17 %. In the 500 mg BID group, only 9.6 % of patients without a history of diabetes or glucose impairment had post-baseline glucose measurements that exceeded 250 mg/dL at least twice. Interstitial lung disease did not occur. Additional data on the clinical efficacy of rociletinib in patients without and with a history of CNS metastases continue to be generated in TIGER-X and the other TIGER studies. ■

Interview: Filippo de Marinis, MD, PhD, Director of the Thoracic Oncology Division at the European Institute of Oncology (IEO), Milan, Italy

"Liquid biopsy is a revolution"

Filippo de Marinis, MD, PhD, Director of the Thoracic Oncology Division at the European Institute of Oncology (IEO), Milan, Italy

What changes in practice have been brought about by the recent advances in the treatment of lung cancer?
In the context of progress obtained in the field of precision medicine in the last 10 years, the assessing of molecular differences between patients allows for a personalised approach, which means that the efficacy of the treatments is approximately three times that of treatments without any mutational selection. The anti-EGFR strategies have completely changed the face of treatment, because these mutations show the greatest incidence globally, and many trials have been conducted in this field. A patient with an *EGFR*-mutated tumour who receives anti-EGFR treatment can survive for more than 30 months. On the other hand, for a patient with adenocarcinoma without mutation, survival ranges between 8 and 10 months. Also, the quality of life is very high with treatment that consists of a pill that is taken daily at home. Here, we see large differences compared to chemotherapy, also with regard to toxicity.

Can you observe the same benefits in your own patients as shown in the trials?
Yes, and these benefits are even improved upon. Registration trials on EGFR inhibitors use the RECIST criteria, which are radiological criteria. In clinical practice, however, we use a broader evaluation, which is not confined to radiological criteria. We do not consider a progression of 2 millimetres, for instance, as an indication for discontinuation of treatment, and we continue to use local treatment. This way, the benefits achieved in the registration studies are almost doubled in practice.

Are new treatments being implemented in the real-world setting to a sufficient degree?
Precision medicine is based on genomic alterations. Up to now, molecular testing has been exclusively performed on tissue samples, but it is not possible to obtain tissue and receive this information in all cases. In nearly 40 % of patients, *EGFR* mutation or *ALK* rearrangement testing is impossible at the time of diagnosis of an adenocarcinoma of the lung. Not all hospitals are linked to distinguished molecular laboratories, and the time that elapses until the results come back varies between 6 or 8 working days in some academic centres, and 20 days in the south of Europe. The oncologist might decide to start chemotherapy treatment without waiting for the results, according to the degree of symptoms.

On a scientific level, are there currently any trends that are particularly promising?
One of the most interesting developments in the diagnostic field is liquid biopsy, which we have started to use at the European Institute of Oncology in Milan. Mutations can be diagnosed based on blood samples within 2 hours. To my mind, this is a revolution, because patients that have not yet benefited from modern treatments due to the issues involved in biopsy assessment can be prescribed targeted therapy thanks to liquid biopsy. It is estimated that more than one third of patients would be eligible for biologicals but are not being treated with the right drug. To date, there are two academic centres in Milan that perform this kind of test, but I am confident that this proportion will swiftly increase. Also, the costs of liquid biospy are moderate, which will contribute to this development.

With regard to treatment, immunotherapy is of course promising, but I think that some additional data is called for to select those patients who will particularly benefit from the treatment. It is not certain that immunotherapy works for all patients, which means that we have the same problem as with the targeted agents. The significance of the PD-L1 expression levels has been investigated, but trials have yielded conflicting results. Different assays for the measurement of PD-L1 levels are being used by different companies. This is a debated problem. Nivolumab was ap-

proved in the second-line setting in patients with squamous histology independent of biomarker expression. For patients with adenocarcinoma, on the other hand, the CheckMate 057 study showed that those expressing PD-L1 experienced higher efficacy of nivolumab than those without PD-L1 expression. We need more trials to clarify whether PD-L1 is the ideal biomarker. Also, the costs of immunotherapy must be taken into account. Selecting patients by means of biomarkers is of course cost-saving.

Which molecular targets are of particular interest?

At present, the story of molecular targeting is the story of *EGFR* mutation and *ALK* translocation. Second-generation ALK inhibitors such as ceritinib and alectinib offer better results compared to those achieved with the first-generation ALK inhibitor crizotinib. Recently, ceritinib was registered in the US by the FDA and in Europe by the EMA for the treatment of patients with *ALK*-positive advanced NSCLC after failure of crizotinib. The phase III ALEX trial is currently evaluating alectinib in the first-line setting of advanced *ALK*-positive NSCLC, in comparison to crizotinib.

For EGFR, second-generation and third-generation inhibitors are being tested. Rociletinib and AZD9291 have shown positive phase I and phase II results in patients expressing the T790M mutation resistance. With these agents, it is possible to obtain survival results similar to those observed in first line treatment. Therefore, a chemo-free schedule is being designed that includes second-line treatment with a biological after a first-line biological. This is of importance for the patients, as chemotherapy is not very popular with them.

Will chemotherapy disappear in the long run?

No. It will be possible to increase the percentage of patients treated without chemotherapy, but I do not think that chemotherapy will disappear from the schedules in the next 10 years. Research efforts will focus on combinations of chemotherapy with other options. ■

Pivotal results and sub-analyses in the field of immunotherapy

CheckMate 017: favourable quality-of-life outcomes

Binding of the inhibitory receptor PD-1 to its ligands, PD-L1 and PD-L2, inhibits T-cell responses. This pathway can be exploited by tumours to escape T-cell-induced anti-tumour activity. Therefore, it is a target for antibodies designed to block this mechanism, with the aim of enhancing immune responses. The fully human anti-PD-1 antibody nivolumab has already been approved in the US and Europe for use in pre-treated patients with advanced squamous NSCLC. In the phase III CheckMate 017 study, nivolumab demonstrated superior OS compared with docetaxel in this population (9.2 vs. 6.0 months; HR, 0.59; p = 0.00025) [1]. This also applied to PFS (3.5 vs. 2.8 months; p = 0.0004).

One of the predefined secondary endpoints of CheckMate 017 was improvement of symptoms. The results of this analysis were presented at the ECC, together with those of an exploratory quality-of-life analysis that included patient-reported outcomes using the EuroQoL-5 Dimensions (EQ-5D) Utility Index and the EQ-5D visual analogue scale [2]. Nivolumab was superior to docetaxel according to both scales. On treatment, changes for nivolumab indicated stable or improved health status, while changes for docetaxel suggested stable or declining health status. In patients treated with docetaxel, their health status deteriorated at a significantly faster rate than for the patients on nivolumab. Symptom burden according to the Lung Cancer Symptom Scale was stable from baseline in patients remaining on treatment with docetaxel, but improved meaningfully in those remaining on nivolumab (Figure 1).

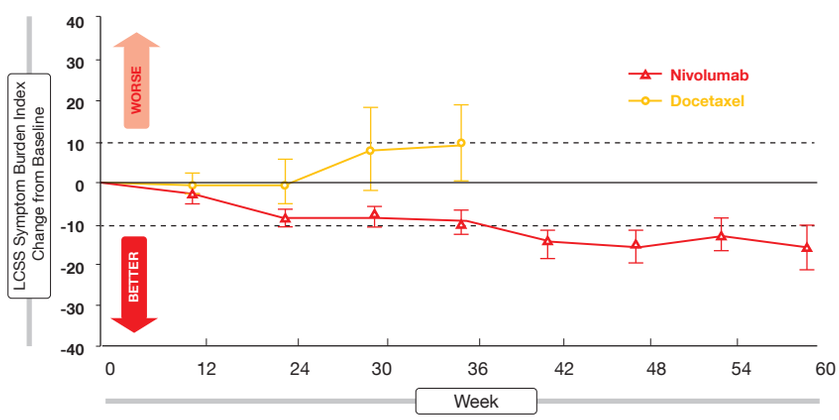

Figure 1: Symptom burden on treatment with nivolumab versus docetaxel

Eighteen-month update of CheckMate 057

For patients with advanced non-squamous NSCLC, the phase III, randomised CheckMate 057 trial also demonstrated the superiority of nivolumab over doc-

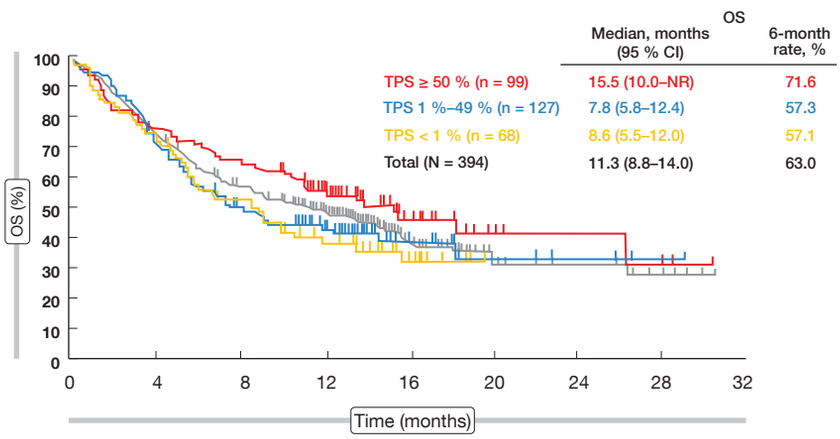

Figure 2: Overall survival according to tumour proportion score in the pembrolizumab 10 mg cohort of KEYNOTE-001

etaxel. In this pre-treated cohort, the immunotherapeutic agent conveyed benefits with regard to OS (12.2 vs. 9.4 months; HR, 0.73; p = 0.0015) and ORR (19 % vs. 12 %; p = 0.0246) [3]. OS rates at 1 year were 51 % and 39 %, respectively. The biomarker analysis showed a correlation between PD-L1 expression and OS, as well as PFS.

The 18-month update continued to favour nivolumab treatment, with OS rates of 39 % versus 23 % [4]. This difference translated into a 28 % reduction in mortality risk (HR, 0.72), which was highly significant (p = 0.0009). According to subgroup analysis, the ORRs were superior for nivolumab in all subsets, with the exception of never smokers and *EGFR*-positive patients. As in the primary analysis, nivolumab demonstrated clinical benefit in patients expressing PD-L1. Depending on the degree of expression, the median OS ranged from 17.7 months to 19.9 months with nivolumab (vs. 8.0 to 9.0 months with docetaxel), whereas in non-expressors, survival outcomes did not differ between the two treatment arms. Response rates also favoured nivolumab (31 % to 37 %) over docetaxel (12 % to 13 %) in the patients expressing PD-L1. In PD-L1–negative patients, on the other hand, the ORR was slightly higher with docetaxel than nivolumab. The median duration of response was longer for nivolumab in both expressors (16.0 vs. 5.6 months) and non-expressors (18.3 vs. 5.6 months).

Patient-reported outcomes were assessed according to the Average Symptom Burden Index. By week 12, symptom improvement rates were similar for nivolumab and docetaxel, at 17.8 % and 19.7 %, respectively. Lung Cancer Symptom Scale scores remained stable throughout treatment, in both arms.

Rapid tumour reduction with pembrolizumab: KEYNOTE-001

Two doses of the humanised anti-PD-1 antibody pembrolizumab were tested in the KEYNOTE-001 trial in 449 previously treated patients who suffered from advanced NSCLC of any histology [5]. The analysis showed similar efficacy and safety with pembrolizumab 2 mg/kg and 10 mg/kg, supporting 2 mg/kg every three weeks as an effective dose in NSCLC. The correlation of efficacy with PD-L1 expression was assessed on the basis of tumour samples that were scored according to the percentage of tumour cells with membranous PD-L1 staining (tumour proportion score; TPS).

Indeed, tumour shrinkage was more pronounced in patients showing PD-L1 TPS ≥ 50 % compared to those with PD-L1 TPS < 50 % (74.2 % vs. 51.7 %). ORR was highest in the PD-L1 TPS ≥ 50 % cohort in both dose groups. While tumour size at baseline did not affect ORR, responses were observed less frequently in patients with liver metastases (13.6 %) than in those without (21.2 %). Rapid tumour reductions occurred predominantly in the cohort with TPS ≥ 50 %; also, the duration of response was longest in this subgroup. Correspondingly, patients with TPS ≥ 50 % benefited most with regard to OS, as they experienced median survival of 15.5 months in the 10-mg dose group (Figure 2). The same correlation applied to PFS: at 6 months, 49.9 % of those with TPS ≥ 50 % were progression-free, compared to 25.3 % and 23.2 % in the groups with TPS 1 % to 49 % and < 1 %, respectively. Overall, PD-L1 TPS ≥ 50 % was identified as a marker for patients with the greatest likelihood to derive benefit from pembrolizumab treatment. Randomised data will be generated in the ongoing KEYNOTE-010 study that is evaluating pembrolizumab 2 mg/kg or 10 mg/kg three-weekly compared to docetaxel.

Is PD-L2 expression important?

A laboratory analysis addressed the potential relevance of PD-L2, one of the two known binding partners of PD-1, with respect to the efficacy of anti-PD-1 therapies in various cancers, such as pembrolizumab [6]. PD-L2 negatively regulates T cells in immune responses. Some tumours show documented PD-L2 expression by tumour cells and/or infiltrating immune cells. PD-L2 has a role in mediating the severity of disease in murine models of autoimmunity, hypersensitivity and infection.

Archival samples obtained from pembrolizumab-treated patients with a range of tumours, among them NSCLC, were evaluated. PD-L2 expression was found in various degrees on tumour cells, stromal cells, and endothelium. In NSCLC, stromal cell expression outweighed both tumour cell and endothelial expression. PD-L2 and PD-L1 expression were generally concurrent, although discordance was observed in both directions. Notably, some NSCLC samples showed PD-L1 expression in the absence of PD-L2. However, as for the other tumour types, the agreement was highly significant. A pilot analysis in patients with squamous-cell carcinoma of the head and neck suggests that PD-L2 status predicts the outcome on pembrolizumab treatment after adjusting for the impact of PD-L1 expression.

Primary analysis of POPLAR

By inhibiting PD-L1 instead of PD-1, additional benefits can be gained, because this approach leaves the PD-L2/

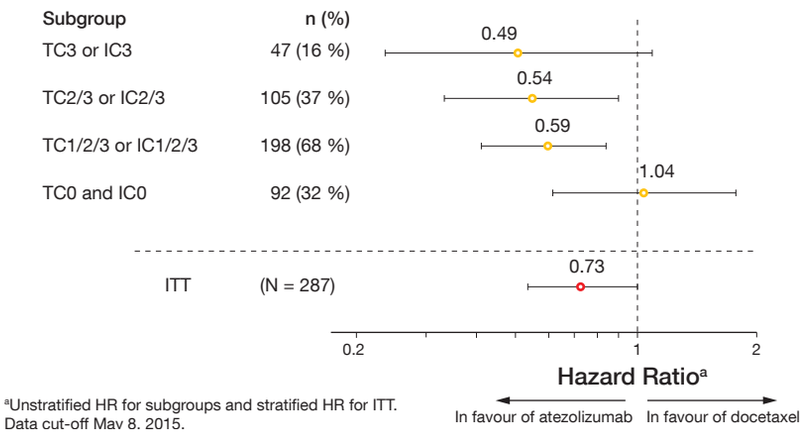

Figure 3: Overall survival according to PD-L1 expression in POPLAR (atezolizumab vs. docetaxel)

PD-1 interaction intact, thus potentially preserving peripheral homeostasis. The humanised anti-PD-L1 antibody atezolizumab works through inhibition of the binding of PD-L1 to PD-1 and B7.1. This mechanism can restore anti-tumour T-cell activity and enhance T-cell priming. The interim analysis of the randomised phase II POPLAR study demonstrated promising ORR with atezolizumab monotherapy in the second-line and third-line treatment of metastatic or locally advanced NSCLC, as compared to docetaxel [7]. This effect correlated with PD-L1 expression on tumour cells (TC) and/or tumour-infiltrating immune cells (IC). Expression was defined according to four cut-off levels (0 to 3 for both TC and IC), and four cohorts were investigated (TC0 and IC0; TC1/2/3 and IC1/2/3; TC2/3 and IC2/3; TC3/IC3).

The primary analysis presented at ECC showed significant OS improvements in both squamous and non-squamous NSCLC [8]. Median OS in the entire cohort was 12.6 versus 9.7 months with atezolizumab and docetaxel, respectively (HR, 0.73; p = 0.040). Again, the results were in favour of atezolizumab in patients expressing PD-L1 on TC or IC, with higher expression indicating improved OS (Figure 3). The same correlation applied to PFS and ORR. Both TC and IC expression were shown to be independent predictors of survival improvement with atezolizumab. Duration of response was 14.3 versus 7.2 months with atezolizumab and docetaxel, respectively. The safety profile of atezolizumab was consistent with previous studies and compared favourably to chemotherapy. Several ongoing trials are assessing atezolizumab in various settings.

BIRCH: atezolizumab in a PD-L1–enriched cohort

In contrast to POPLAR, the single-arm, phase II BIRCH trial tested atezolizumab in a PD-L1–selected NSCLC population [9]. PD-L1 expression was tested using immunohistochemistry (IHC); only patients with TC2/3 or IC2/3 were included in the study. Three cohorts of patients with locally advanced or metastatic tumours received atezolizumab as first line (Cohort 1) or as subsequent lines (Cohort 2: one prior platinum chemotherapy; Cohort 3: at least two prior chemotherapies, including one platinum-containing regimen). The primary endpoint was ORR, according to the Independent Review Facility.

BIRCH met its primary endpoint in all of the predefined subgroups. ORR was highest in patients with maximum TC or IC expression (TC3, IC3) in all lines. The OS data are not yet mature, but the 6-month OS rates were shown to be consistent with the POPLAR results for the second-line and third-line setting. In the TC2/3 and IC2/3 cohorts, OS was 76 % and 71 % at 6 months for second and third line, respectively. In the TC3 and IC3 cohorts, it was 80 % and 75 %, respectively. The majority of adverse events were grades 1 or 2, and no unexpected safety signals occurred. ■

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Interview: Riyaz Shah, PhD, FRCP, Kent Oncology Centre, Maidstone Hospital, Maidstone, UK

"Immunotherapy has opened up a new avenue of research"

Riyaz Shah, PhD, FRCP, Kent Oncology Centre, Maidstone Hospital, Maidstone, UK

The treatment of lung cancer has advanced considerably in the last few years. Which of these advances would you deem most important from the clinical point of view?

We think of lung cancer as a generic term, but actually it is a term that encompasses many different diseases. *EGFR*-mutated lung cancer, squamous lung cancer, and *ALK*-positive lung cancer are completely different diseases with different biologies and different behaviours. Within each of the main subtypes of lung cancer, huge advances are being made. From my point of view, this year's most exciting data is the activity of immune checkpoint inhibition in squamous lung cancer that was shown in the CheckMate 017 trial presented at the ASCO Congress. These were landmark results that are practice changing. Within a few weeks of that data being presented, an expanded access programme became available in the UK, and I started to prescribe nivolumab to patients. I have seen some absolutely dramatic responses; the course of disease was completely changed with that PD-1 antibody in some very sick patients. An area with a very high unmet need is also small-cell lung cancer, where immunotherapy shows promise as well. Immunotherapy has opened up a whole new avenue of research in cancer treatment. Many other drugs are being developed, and combinations of these with CTLA-4 antibodies are being tested. Also, investigations are ongoing in the adjuvant setting. Of course, these drugs are expensive. I work in the UK, where access to new drugs is not always straightforward, but my preliminary experience has been very encouraging. New understanding of the side effects is constantly emerging, which is the one concern I have.

One of the other exciting new areas is our understanding of acquired resistance in *EGFR*-mutated lung cancer. Data with the new third-generation inhibitors rociletinib and AZD9291 are being presented. Overall, there are developments in almost every facet.

Are new treatments being implemented in the real-world setting to a sufficient degree?

I think the problem with new treatments is that there are all sorts of different issues, such as the country you work in. Each country has its own regulatory process, its own funding pathway, and its own way of managing health care. That means there is a wide variation in practice around the world. The main issue that we have in the UK is the cost of the drugs and the fact that it is a socialised health-care system that has a finite set of resources. It is therefore very difficult to fund some of the latest drugs for all cancers. The developments that are going on in lung cancer are also going on in colorectal cancer, in breast cancer and in all the other malignancies. All of these drugs need to be funded. However, the real-world limitation is not just about money. The ability of oncologists to keep up-to-date is being stretched now because of the increasing complexity. It is very difficult for a busy oncologist to even know all of the options that are available. Also, the treatment has to be delivered, which calls for chemotherapy units, trained nurses, support staff and primary care professionals who know what to do once side-effects occur. Overall, it is a huge, complex web that needs to be developed, and this will be a big challenge for the world.

Can you observe improved survival in your patients as a result of new treatments?

I can definitively answer that as a yes. Junior doctors who come to my lung cancer clinic almost always comment within the first week that they cannot believe that all these patients are alive. They are patients with stage-IV lung cancer, who have druggable mutations and who have been alive with a range of treatments for 2 or 3 years, or sometimes even up to 4 or 5 years. We just did not observe that 5 or 10 years ago. Of course we need to appreciate that there is a huge drop-off; many patients die very quickly after diagnosis, so a certain selection bias applies to the survivors, but there can be no doubt that things have improved considerably. Patients with brain metastases, for example, are now able to have resections or stereotactic radiotherapy, and they live for much, much longer periods of time.

Which molecular targets deserve the greatest attention at present?

To my mind, the degree of benefit demonstrated in lung cancer with immunotherapy means that this is the area where we really need to try and improve upon what we already know. There may well be combinations of drugs that will give even greater benefits. However, it is a very complex area. There are a multitude of similar drugs that are being developed by different companies with different biomarkers looking at different subgroups of patients.

Will new findings change the future of lung cancer prevention and early detection?

There is a lot of really interesting emerging data about screening and early detection of lung cancer. We now have irrefutable evidence that screening will identify patients with lung cancers early. If some sort of national and international screening system is established, I am confident that we will be able to detect more cases earlier and give people curative treatment when they are able to receive it.

Which patient characteristics must be taken into account for treatment decisions?
The key aspect about treating patients with cancer is their performance status. The treatment I prescribe is mostly chemotherapy, and patients have to be fit enough for that. Otherwise, things are made worse for them. In addition, the patients' wishes are important. Some are not that interested in survival. They are often quite elderly and want nature to run its course. Others are willing to go to any lengths for even small benefits. I think that it is part of the physician's job to assess how far your patients want to go, and to give them the best within their wishes. Someone who does not want treatment should not be treated.

What will happen to chemotherapy in the long run?
Chemotherapy is a very, very effective treatment for lung cancer. It improves survival, helps the patients maintain their quality of life, and reduces tumour-related symptoms. Even if new drugs replace chemotherapy as a first-line treatment, it will still be there as a second-line or third-line treatment. It will always be there. ■

Lung cancer screening: diagnosis in the nick of time

Lung cancer is the leading cause of cancer mortality worldwide. Only 16 % of patients survive for 5 years, compared to 89 % with breast cancer and almost 100 % with prostate cancer. Likewise, only 16 % of patients with lung cancer are diagnosed before the disease has spread (vs. 60 % with breast cancer and 90 % with prostate cancer). "Once symptoms develop, it is too late", emphasised Giulia Veronesi, MD, Division of Thoracic Surgery, European Institute of Oncology, Milan, Italy.

In contrast to breast and prostate cancer, identification of early lung cancer is not part of established screening programmes. As Dr. Veronesi noted, screening with low-dose computed tomography (LDCT) should be urgently implemented in Europe. LDCT has been shown to be superior to X-rays for the detection of NSCLC. "It is a non-invasive tool, and the examination can be performed quickly and at low cost, without the use of contrast medium."

Lung cancer mortality is reduced by LDCT screening, as surgery then offers the prospect of cure in an earlier stage. The 10-year survival rate for resected stage I cancer is as high as 92 % [1]. "Diagnostic algorithms allow for a safe screening process and low numbers of resections for benign disease", stated Dr. Veronesi. In a study on the distribution of lung cancers according to volume doubling time, 10 % of screened tumours were overdiagnosed, meaning that these tumours grew so slowly that they would not have affected the life expectancy of the patients, as they showed a volume doubling time of more than 600 days [2]. Optimal selection of the high-risk target population and correct screening intervals can be achieved by use of validated risk models. Also, cost-effectiveness of lung cancer screening has been established: "These costs are lower than those of breast screening."

Large-scale assessment of early detection

A number of cohort studies have investigated the usefulness of screening, including the Early Lung Cancer Action Program, the Anti-Lung Association Project in Tokyo, Japan, the Nagano Population-Based Lung Screening Trial, the NELSON Trial, the Italian Lung Cancer CT Screening Trial, the Multicentric Italian Lung Detection Trial, the German Lung Cancer Screening Intervention Study, the Danish Lung Cancer Screening Trial, and the United Kingdom Lung Cancer Screening Trial. In the US, the National Lung Screening Trial was the largest randomised controlled trial of LDCT screening for lung cancer (n = 53,454) [3]. People with high risk for lung cancer were randomly assigned to undergo three annual screenings with either LDCT or chest radiography. The trial achieved its goal of showing that the stated mortality reduction threshold of 20 %, which was required to provide national screening, was reached with LDCT as compared to radiography (Figure). "The results led to the acceptance of screening in the US," noted Claudia Henschke, PhD, MD, Head of the Lung and Cardiac Screening Program, Mount Sinai Medical Center, USA.

Aggressive smoking cessation programmes increase the effectiveness of screening and should therefore be fully integrated into all screening programmes. This implies that optimum smoking cessation techniques must be identified. Also, registries are needed for continued improvement and quality assurance. "More nimble methodology for assessing new potential screening tests is called for", said Dr. Henschke. Collection of biological samples (blood, sputum, urine, buccal cells) for future integration into screening is important. ■

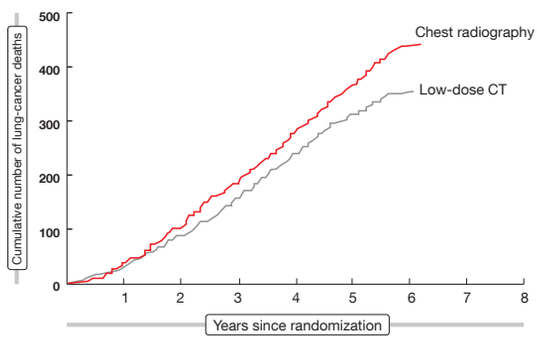

Figure: Lung-cancer-related mortality after radiographic *versus* low-dose computed tomography (CT) screening in the National Lung Screening Trial

Source: Special Session: Lung Cancer Screening and Prevention, 26th September, 2015

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Genomic testing – becoming part of everyday practice

Next-generation sequencing: robust and reliable

Network Genomic Medicine (NGM), a large healthcare-provider network that involves over 220 lung cancer centres in Germany, was established with the goal of nationwide implementation of personalised medicine and molecular treatments [1]. Over 5,000 comprehensive next-generation sequencing (NGS)-based lung cancer tests are provided each year, whereby testing and counselling is performed centrally, followed by decentralised treatment. A clinical trial platform is attached to NGM. However, on the whole, test rates are still lagging behind. In 2014, the test rate for *EGFR* mutations in Germany was low, at approximately 52 %. This corresponds to 3,454 life years that were lost without appropriate treatment.

To date, the histopathological data of 6,210 lung cancer patients have been assessed. The Figure shows the distribution of genetic alterations in non-squamous and squamous NSCLC. In squamous-cell carcinoma, 68 % of the cases were wild-type, and *FGFR1* mutations were found in 19 %. The current outcome data confirm survival benefits gained by the use of targeted treatment. For patients with *ALK* rearrangement or *EGFR* mutation, median OS was 35 and 29 months, respectively. In contrast, those with wild-type tumours had a median OS of 11 months. In patients with *BRAF* mutations or HER2-positive tumours, a median OS of 23 and 25 months was observed, respectively. Furthermore, the analysis demonstrates that patients included in clinical trials have a significantly better prognosis than those treated outside of trials. For instance, *EGFR*-mutated patients receiving third-generation *EGFR* inhibitors lived for a median of 55 months (vs. 22 months in patients outside of trials; p = 0.002).

Cost-covering NGS is now available for about 35 % of all German lung cancer patients within the NGM. A comparison of NGS with Sanger sequencing yielded a significant difference in favour of NGS. NGS provides reduction in turnaround time, with the assessment of an entire panel (14 genes) taking 12 days, while the assessment of 4 genes with Sanger sequencing takes 10 days. NGS is highly sensitive for co-occupied and rare mutations, and for detection of resistance. Moreover, its cost is fixed and transparent, compared to the multiplication of single-test costs.

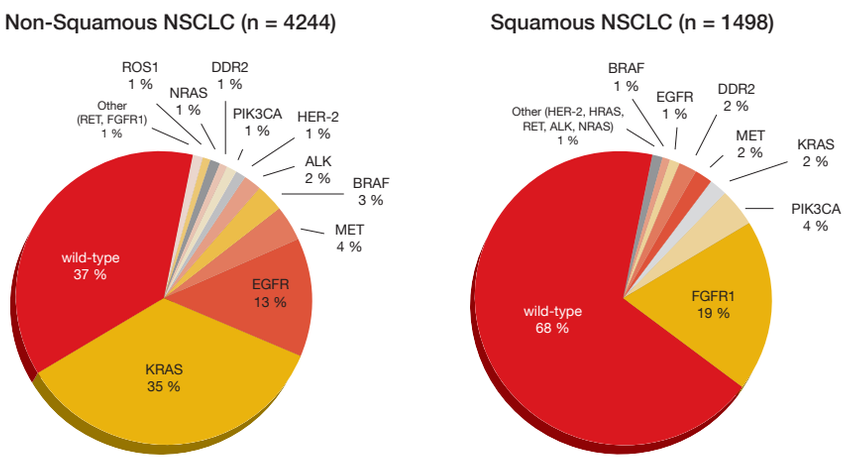

Figure: Gene alterations in non-squamous and squamous NSCLC

Spectrum of *BRAF* mutations in lung cancer

Over the last decade, oncogenic drivers in lung cancer have been identified, but only a subset is mentioned in consensus guidelines. One of these is the $BRAF^{V600E}$ mutation, which suggests potential benefit from molecularly targeted therapy. Non-$BRAF^{V600E}$ alterations are seen in lung cancer as well, and are thought to be involved in oncogenesis. However, previous studies did not differentiate between $BRAF^{V600E}$ and other mutations.

A study presented at ECC used a hybrid capture NGS-based comprehensive genomic profiling (CGP) integrated assay to identify the nature of *BRAF* alterations in lung cancer [2]. For this analysis, 3,300 lung carcinoma cases were tested by CGP in the course of clinical care. The genomic profiles were analysed by histological type, alterations within *BRAF*, and other co-segregating alterations. Approximately 50 % of specimens were obtained at metastatic sites. Two thirds of the patients had been diagnosed with adenocarcinoma. Squamous-cell carcinoma was present in 11 %, and small-cell lung cancer (SCLC) in 6 %. Sixteen percent were classified as NSCLC-NOS (not otherwise specified).

Within this population, 4.6 % of patients harboured *BRAF* mutations, which were found to be enriched in adenocarcinoma (6.1 %). More than half of the alterations in adenocarcinoma belonged to the non-*V600E* category. Squamous-cell carcinoma harbours *BRAF* alterations in 0.8 %; none of these were $BRAF^{V600E}$. In patients with NSCLC NOS, *BRAF* alterations were found in 3.2 %, with 85 % falling into the non-*V600E* category. No *BRAF* mutations were observed in SCLC. Certain other genomic alterations, such as TP53, SETD2, and STK11, tended to co-segregate with *BRAF* alterations. *BRAF* fusions, which appear to confer susceptibility to MEK inhibitor treatment in metastatic melanoma, were only rarely observed. ■

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Optimising treatment in local and regional lung cancer

Prediction of node negativity with a view to sublobar resection

As patients with node-negative early lung cancer might be ideal candidates for sublobar resection, predictors of pathological node-negative disease were investigated in a cohort of patients with clinical stage IA NSCLC [1]. These included 502 patients with adenocarcinoma and 100 with squamous-cell carcinoma from four institutions. The relationship between lymph node status and preoperative factors, such as tumour size according to high-resolution computed tomography (HRCT) and the maximum standardised uptake value (SUVmax) on fluorodeoxyglucose positron emission tomography (FDG-PET/CT), was examined.

In the adenocarcinoma cohort, SUVmax on FDG-PET/CT and tumour size on HRCT may be useful to predict node-negative stage IA lung cancer. When solid tumour size was < 0.8 cm or SUVmax was < 1.5 (N0 criteria), approximately 50 % of patients with stage cT1 disease had no affected lymph nodes (Table). Sublobar resection was shown to be feasible in stage IA tumours that meet N0 criteria, as relapse-free survival and overall survival (OS) did not differ between patients treated with lobectomy or sublobar resection.

For patients with squamous-cell carcinoma, no independent predictive factors for lymph node metastasis were identified. In particular, tumour size on HRCT and SUVmax on FDG-PET/CT were not predictive of lymph node status in IA carcinoma.

IASLC/ATS/ERS classification and benefit from adjuvant therapy

A retrospective study evaluated whether subtypes according to the 2011 International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification are predictive for benefits derived from adjuvant chemotherapy in patients with resected stage IB lung adenocarcinoma [2]. All of these patients had undergone complete resection with mediastinal lymph node dissection or sampling. Adjuvant chemotherapy was not given in a randomised manner, but was used according to the physician's choice.

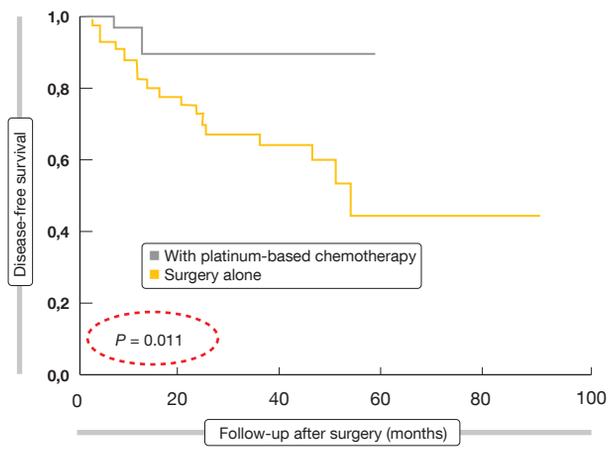

Figure: Improved disease-free survival with platinum-based chemotherapy versus surgery alone in patients with a micropapillary/solid subtype

Out of 359 patients, 137 (38.2 %) had received adjuvant therapy, which consisted of platinum-based doublet chemotherapy in 54 % of cases. Forty-two percent were treated with oral tegafur-uracil, and 4.4 % received EGFR tyrosine kinase inhibitor therapy. The platinum-based doublet chemotherapy regimens contained docetaxel, vinorelbine and gemcitabine. In the group of patients who were treated with adjuvant chemotherapy, female gender, tumour size of > 3 cm, and a predominantly micropapillary/solid pattern were found significantly more frequently as compared to those who only underwent surgery.

Indeed, tumour size > 3 cm and micropapillary/solid predominant pattern were identified as factors that significantly decreased survival. In patients receiving surgery alone, the lepidic/acinar/papillary predominant pattern was associated with a significantly longer OS (p = 0.027) and disease-free survival (DFS; p = 0.001) compared to the micropapillary/solid predominant pattern. In contrast, in patients treated with adjuvant chemotherapy, neither the micropapillary/solid predominant pattern nor the lepidic/acinar/papillary predominant pattern were predictive of OS and DFS. Interestingly, in patients with the micropapillary/solid predominant subtype, adjuvant platinum-based chemotherapy significantly improved DFS (p = 0.011) and tended to improve OS (p = 0.055) compared to surgery alone (Figure). In contrast, patients with the lepidic/acinar/papillary predominant subtype did not derive any benefit from adjuvant platinum-based chemotherapy.

The researchers concluded that the IASL/ATS/ERS classification may have a significant predictive value with regard to potential benefits from adjuvant therapy in stage IB lung adenocarcinoma. However, prospective multi-institutional studies and randomised clinical trials are mandatory to further validate these results.

Mutation patterns across lung cancer

The prevalence and clinical association of gene mutations were investigated in the ETOP Lungscape Project, in which 17 centres that are mainly located in Europe participated [3]. A total of 2,709 surgically resected, stage I to III NSCLC patients constituted the Lungscape Tu-

TABLE
Number of patients without nodal metastasis according to solid tumour size, SUVmax, and their combination

	cT1 (n = 502)	cT1a (n = 289)	cT1b (n = 213)
Solid tumour size < 0.8 cm	187 (37.3 %)	131 (45.3 %)	56 (26.3 %)
SUVmax < 1.5	206 (41.0 %)	138 (47.8 %)	68 (31.9 %)
Solid tumour size < 0.8 cm or SUVmax < 1.5	255 (50.8 %)	169 (58.5 %)	86 (40.4 %)

mour Cohort. In the study presented at the ECC, the prevalence of selected cancer-related mutations, their interrelationships, the correlation of the mutation patterns with other molecular alterations, as well as outcome of the patients were determined. Multiplex mutation testing was applied in 1,801 patients, whose median follow-up after surgery was 4.7 years. Gene mutation testing was conducted using Fluidigm technology. The Fluidigm Gene Panel is designed to reveal multiple cancer indications, including for lung cancer. The functionally relevant genes related to lung cancer include *EGFR, KRAS, ERBB2, BRAF* (V600E/K), *PIK3CA* (L755P) and *AKT1* (E17K). The roles of *ERBB2, BRAF, PIK3CA* and *AKT1* mutations in anti-cancer therapies remain to be established.

In the entire cohort, *KRAS* was the most frequent mutation (23.1 %), followed by *MET* (6.8 %), *EGFR* (5.2 %) and *PI3KCA* (4.6 %). The other mutations had very low prevalence. According to the histology, adenocarcinoma is associated with a much higher prevalence of *KRAS* mutations (38.0 %) than squamous-cell carcinoma (6.2 %). For *PIK3CA*, the distribution was reversed (3.3 % and 6.4 %, respectively). *EGFR* mutations were more frequent in never smokers than in current or former smokers (19.7 % versus 3.3 %).

KRAS and *EGFR* mutation prevalence was higher in females, patients with adenocarcinoma, and smaller tumour size. In patients diagnosed with *PIK3CA* mutation, tumour size tended to be larger, and the histology was predominantly squamous-cell carcinoma. The well-known mutual exclusivity between *KRAS* mutation and *EGFR* mutation was confirmed. MET status showed an association with *KRAS* and *EGFR* mutations, but not with *PIK3CA* mutation. The outcome analysis showed no association between relapse-free survival or OS and any of the mutations.

Malignant pleural effusion: Rh-endostatin

Recombinant human endostatin (Rh-endostatin) combined with chemotherapy was assessed in Chinese patients suffering from malignant pleural effusion, both as primary treatment and after failure of previous intra-pleural therapy [4]. Rh-endostatin is a broad-spectrum anti-angiogenesis inhibitor that regulates groups of active proteins involved in angiogenesis, including the expression levels of VEGF-A, FGFR, and HIF-1α. In this trial, Rh-endostatin was administered by means of intracavitary injection together with cisplatin, while the control group received cisplatin only.

The ORR, which was defined as the primary endpoint, was significantly in favour of the combination (76.4 % vs. 55.0 %; $p < 0.05$). This was accompanied by a significantly greater improvement in Karnofsky performance status (88.0 % vs. 60.0 %; $p < 0.05$). With regard to AEs, patients receiving Rh-endostatin plus cisplatin experienced higher rates of neutropenia, anaemia, diarrhoea, fatigue and rash, but none of these differences were significant. No grade 3/4 AEs were observed. The authors concluded that the combination has promising efficacy that is superior to cisplatin alone. ■

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Small-cell lung cancer: established and novel approaches

Small-cell lung cancer (SCLC) accounts for 14 % of all lung cancers. It is initially sensitive to chemotherapy and radiation therapy, but resistance tends to develop rapidly, which leads to high recurrence rates. Outcomes with second-line treatments are poor, with 5-year survival rates of only 5 %. Topotecan is the only approved agent in the second-line setting.

The phase I/II CheckMate 032 trial evaluated nivolumab as monotherapy and in combination in various tumour types, including SCLC. The updated results for the SCLC cohort that were presented at the ECC showed that both nivolumab monotherapy and the combination of nivolumab and ipilimumab have anti-tumour activity in patients who have progressed after at least one prior therapy, including a platinum-based regimen as first line [1]. The patients were unselected in terms of PD-L1 expression. Nivolumab monotherapy

was administered at a dose of 3 mg/kg very 2 weeks (n = 80). The combination was applied every three weeks for 4 cycles at three different doses (nivolumab 1 mg/kg plus ipilimumab 1 mg/kg [n = 3]; nivolumab 1 mg/kg plus ipilimumab 3 mg/kg [n = 47]; nivolumab 3 mg/kg plus ipilimumab 1 mg/kg [n = 53]). Approximately one third of patients was platinum-resistant/ refractory.

Benefits irrespective of platinum sensitivity

Responses were durable and occurred early on. The ORR, which was defined as the primary outcome, was 12.7 % in the nivolumab monotherapy arm and 31.1 % in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg arm (Table). Objective responses were observed in second-line patients with both platinum-sensitive and platinum-resistant disease. Median OS were 3.55 months and 7.75 months, with 27.1 % and 47.5 % of patients alive at 1 year. For PFS, median estimates were 1.38 months and 3.35 months for the two regimens. The 9-month PFS rates were 10.2 % and 30.4 %. In both treatment arms, tumour responses were observed in patients with < 1 % and ≥ 1 % PD-L1 expression, according to the preliminary analysis.

Treatment-related AEs occurred more frequently with the combination regimen. Grade 3–4 AEs were seen in 11.3 % of patients in the nivolumab monotherapy arm and 31.9 % of patients in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg arm. Fatigue and diarrhoea constituted the most frequent AEs in both groups. Grade-2 limbic encephalitis occurred in two patients, which resolved with immunosuppressive treatment. One patient had grade 4 limbic encephalitis, which did not resolve with immunosuppressive treatment. The authors therefore recommended close monitoring for early signs or symptoms of paraneoplastic syndromes (e. g., limbic encephalitis) and autoimmune disease (e. g., myasthenia gravis). Pneumonitis was diagnosed in two patients in the monotherapy arm and in one patient in the combination arm. The management of toxicity followed established safety guidelines.

Phase III studies in SCLC patients with extensive stage disease in the first line and second line are presently being initiated; CheckMate 331 is assessing nivolumab versus chemotherapy in relapsed SCLC, and CheckMate 451 is testing nivolumab alone and in combination with ipilimumab as maintenance therapy after platinum-based first-line therapy in SCLC.

TABLE
Clinical activity of nivolumab monotherapy and nivolumab plus ipilimumab

	Nivolumab 3 mg/kg (n = 55)[a]	Nivolumab 1 mg/kg plus Ipilimumab 3 mg/kg (n = 45)[b]
ORR, %	12.7	31.1
Complete response, %	0	2.2
Partial response, %	12.7	28.9
Stable disease, %	16.4	22.2
Disease control rate, %	29.1	53.3
Progressive disease, %	61.8	37.8
Death prior to first response assessment, %	5.5	4.4
Other, %	1.8	2.2
Not reported, %	1.8	2.2
Median time to objective response, months	1.61	2.15
Median duration of response, months (95% CI) range	Not reached (4.40, NR) 4.4-14.1+	6.90 (1.48, not reached) 1.3-9.5+

[a] 25 patients were not evaluable
[b] Two patients were not evaluable

Rova-T: single-agent activity of an antibody drug conjugate

To date, no targeted therapy has shown proven benefit in patients with SCLC. Encouraging phase I data are now available for rovalpituzumab tesirine (Rova-T), a delta-like protein (DLL)3-targeted antibody drug conjugate [2]. DLL3, which is overexpressed in SCLC tumour-initiating cells, is directly targeted by the humanised monoclonal antibody present in Rova-T.

This trial included 73 patients with relapsed and refractory SCLC who had experienced disease progression after first-line or second-line treatment. Escalating doses of Rova-T were administered once every 3 weeks. Confirmed responses were noted at 0.2 mg/kg, 0.3 mg/kg and 0.4 mg/kg. Subsequently, the phase Ib expansion cohorts received 0.2 mg/kg every 3 weeks or 0.3 mg/kg every 6 weeks.

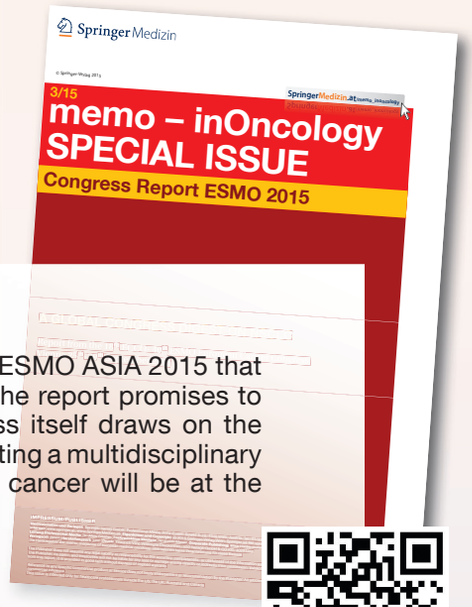
In the group of patients evaluable for response assessment (n = 53), a total of 23 % achieved ORR, with a clinical benefit rate (CBR) of 68 %. Forty-nine samples were obtained for the assessment of DLL3 expression, which was high in approximately 70 % of patients. In this group, ORR was 44 % and CBR 78 %. Importantly, responses were similar regardless of whether Rova-T was administered as second line or third line. Patients experiencing stable disease, on the other hand, showed variable DLL3 expression.

These responses were durable. At the 0.3 mg/kg every 6 weeks dosing schedule, patients had an ongoing response for 189 days after their confirmatory computed tomography. The survival remained prolonged in these patients. Therefore, the 0.3 mg/kg every 6 weeks schedule was chosen as the randomised phase II dose.

Rova-T showed a manageable safety profile. Toxicity was comparable between the two dosing cohorts. Fatigue occurred most frequently, at 28 %, followed by peripheral oedema, rash, thrombocytopenia, pleural effusion, and nausea. Also, photosensitivity reactions occurred in 12 %. Overall, the benefits achieved with Rova-T are exceptional in the second-line and third-line SCLC setting. These results support biomarker-guided phase II studies, as DLL3 might be the first predictive biomarker associated with drug efficacy in SCLC. ■

REFERENCES

1 Calvo E et al., Nivolumab monotherapy or in combination with ipilimumab for treatment of recurrent small cell lung cancer (SCLC). ECC 2015, abstract 3098
2 Pietanza MC et al., Phase I study of a DLL3-targeted antibody drug conjugate, rovalpituzumab tesirine, in patients with relapsed and refractory small cell lung cancer (SCLC). ECC 2015, abstract 7LBA



Forthcoming Special Issue

This special issue will be offering a synopsis from the ESMO ASIA 2015 that will be held in Singapore, in December of this year. The report promises to make for stimulating reading, as the ESMO Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

ESMO ASIA 2015

SINGAPORE, 18–21 DECEMBER 2015

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