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# memo – inOncology SPECIAL ISSUE

## Congress Report ESMO Asia 2015

### A GLOBAL CONGRESS DIGEST ON NSCLC

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# Preface

Dear Colleagues,

My career in lung cancer care started at a time when nihilism prevailed and the standard approach in advanced disease consisted of best supportive measures. No treatments were available in which the benefits outweighed the toxicity. The arrival of chemotherapy eventually rendered improvements in survival possible; in addition, this strategy allowed for symptom relief and increases in quality of life. Platinum-based chemotherapy became the first-line treatment of choice.

For at least a decade, chemotherapy doublets were compared across trials, but none gave rise to superior clinical outcomes as compared to another. Most notably, for patients with advanced disease, cure was still out of reach. It must be kept in mind, however, that all of these trials were performed before the era of molecular testing for driver mutations. Also, selection based on the histological subtype only took hold with the introduction of the VEGF inhibitor bevacizumab, which caused severe toxicity in patients with squamous-cell tumours. Re-examination of previously conducted pemetrexed trials revealed significant beneficial effects of this chemotherapy in non-squamous disease, whereas the subgroup with squamous histology fared even worse with pemetrexed than with the comparator. This was the first example of qualitative interactions, as opposed to quantitative interactions, which describe the magnitude of benefits conveyed by different treatments.

Today, it is common knowledge that numerous molecular changes drive the development of lung cancer. Critical pathways have been identified, and targeted agents have become indispensable players in our arma-

mentarium. Patients can now expect to derive survival benefits from first-line chemotherapy, second-line chemotherapy, and third-line molecularly targeted therapy.

In patients with *EGFR*-activating mutations, the first-line treatment of choice is not chemotherapy, but rather *EGFR* tyrosine kinase inhibitor therapy with erlotinib, gefitinib or afatinib. However, resistance invariably develops, frequently due to emergence of the T790M mutation. Research has found answers to this phenomenon, too; numerous drugs are being tested in the T790M-mutated setting, with promising results.

Nevertheless, the established drugable molecular targets are virtually restricted to adenocarcinoma, and frequently in cancers of lifetime non-smokers. For patients with squamous-cell carcinoma, proven targeted therapies are lacking. The scientific community is called upon to rise to the occasion and identify both driver mutations and resistance mutations upfront, as retrospective analyses of samples are not appropriate any more.

Immunotherapy represents an exciting new option, particularly in patients with squamous cell cancer, and in prior or current smokers. In the CheckMate 017 trial, the PD-1 inhibitor nivolumab provided clinically meaningful and statistically significant overall survival benefit independent of PD-L1 expression in a population of previously treated patients with advanced squamous-cell lung cancer. Similar results have been reported in trials of another PD-1 inhibitor pembrolizumab and the PD-L1 inhibitor atezolizumab, but in these studies, benefit appeared to be limited to patients whose tumours expressed PD-L1.



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The proof of usefulness of these new checkpoint inhibitors marked the beginning of a tremendous change in the therapeutic landscape. Currently immunotherapy is being evaluated in earlier lines of therapy and even in the adjuvant setting, where the goal will be to change the cure rate.

The development in the treatment of lung cancer over the last decades is certainly reason for optimism. Nihilism has given way to great advances. Early detection, enhanced selection of patients, and molecular targeting should contribute to turning the prospect of cure into a realistic option for many patients.

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## EGFR-mutation-positive NSCLC: expanding the data pool for established treatment options

### Subgroup analyses of LUX-Lung 3 and 6

Non-small-cell lung cancer (NSCLC) with activating epidermal growth factor receptor (*EGFR*) mutations represents a defined molecular subset of lung cancer that can be targeted with *EGFR* tyrosine kinase inhibitor (TKI) therapies. Erlotinib, gefitinib and afatinib have been approved as first-line treatment options for *EGFR*-mutation-positive NSCLC. While the first-generation TKIs erlotinib and gefitinib work by reversibly inhibiting *EGFR*, the second-generation TKI afatinib acts as an ErbB family blocker by irreversibly inhibiting a broader range of signalling cascades. The efficacy of first-line afatinib was demonstrated by the two large phase III trials LUX-Lung 3 and 6, which consistently showed superior progression-free survival (PFS) with afatinib as compared to standard platinum-doublet chemotherapy [1, 2]. Also, overall survival (OS) was significantly improved in patients with deletion 19 mutations [3].

According to subgroup analyses of the LUX-Lung 3 and 6 trials presented at the ESMO Asia Congress, the OS findings were consistent across Asian, non-Asian and Japanese patients [4]. In all ethnic subgroups, significant OS improvements of 10 to 15 months were seen for patients with deletion 19 mutations (Table), while median OS did not differ significantly between the treatment arms in those harbouring the L858R mutation.

Likewise, further subgroup analyses of LUX-Lung 3 and 6 established similar efficacies of afatinib treatment in patients aged  $\geq 65$  years and in the general

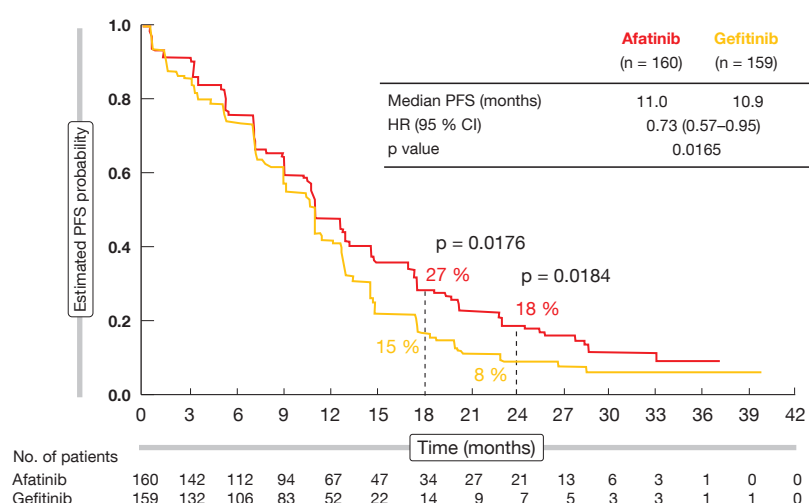


Figure 1: PFS benefit of afatinib as compared to gefitinib in LUX-Lung 7

study population [5]. In LUX-Lung 3, elderly patients experienced significant OS improvement when deletion 19 mutation was present (median OS, 41.5 vs. 14.3 months for afatinib and chemotherapy, respectively; hazard ratio [HR], 0.39;  $p = 0.0073$ ). For LUX-Lung 6, these results were in favour of afatinib as well (34.1 vs. 21.1 months), but not significantly so. The adverse event (AE) profile was comparable to that of the overall population. Based on these results, afatinib can also be considered for patients aged  $\geq 65$  years with advanced *EGFR*-mutation-positive NSCLC.

### LUX-Lung 7: afatinib versus gefitinib in the first-line setting

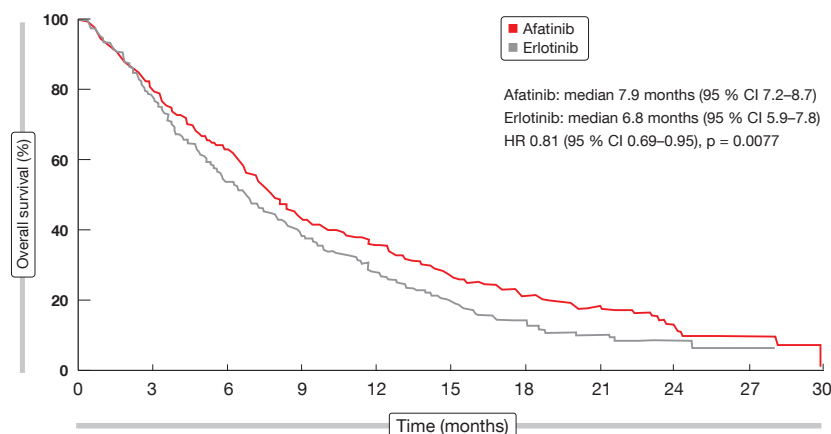
Head-to-head comparisons of first-line TKIs that provide guidance for clinical decision making have been lacking to date. The global, randomised, phase IIB

LUX-Lung 7 trial compared afatinib with gefitinib for untreated patients with IIB/IV adenocarcinoma of the lung and *EGFR* mutation (deletion 19 and/or L858R) [6]. At 64 centres in 13 countries, including North America, Europe, Asia and Australia, participants were randomised to either afatinib 40 mg once daily ( $n = 160$ ) or gefitinib 250 mg once daily ( $n = 159$ ). Treatment beyond progression was allowed if it was deemed appropriate by the investigator. LUX-Lung 7 had three co-primary endpoints: PFS, time to treatment failure (TTF), and OS. The primary analysis of the trial was presented at ESMO Asia 2015.

For the key primary endpoint of PFS (by independent review), the results were significantly in favour of afatinib (median PFS, 11.0 vs. 10.9 months; HR, 0.73;  $p = 0.0165$ ; Figure 1). At 18 and 24 months, marked differences between the two treatment arms emerged. The afatinib-related PFS advantage was seen across the subgroups, and it was not affected by mutation type (deletion 19 vs. L858R mutation) or other factors. With respect to the second co-primary endpoint of TTF, the analysis showed that afatinib-treated patients tended to remain on treatment for longer periods of time (median, 13.7 vs. 11.5 months;

TABLE  
OS by ethnicity in patients harbouring deletion 19

	Median OS for afatinib vs. chemotherapy (months)	HR (95 % CI)	p value
Non-Asian	33.6 vs. 20.0	0.45 (0.21–0.95)	0.031
Asian	31.7 vs. 21.1	0.61 (0.46–0.82)	0.001
Japanese	46.9 vs. 31.5	0.34 (0.13–0.87)	0.018



**Figure 2:** Improvement of OS with afatinib as compared to erlotinib in LUX-Lung 8

HR, 0.73;  $p = 0.0073$ ). This difference is in agreement with the PFS gain. The OS data are still immature and should become available in the course of 2016.

### Response and tolerability outcomes in LUX-Lung 7

Across the afatinib and gefitinib treatment arms, objective responses occurred in 70 % vs. 56 %, respectively ( $p = 0.0083$ ). Also, the median duration of response was longer in the afatinib group than for gefitinib (10.1 vs. 8.4 months). In patients with deletion 19 mutation, afatinib therapy provided marked benefits for PFS (HR, 0.76), response rates (73 % vs. 66 %), and tumour shrinkage. These benefits, however, were even greater in patients with L858R mutation (PFS: HR, 0.71; response rates, 66 % vs. 42 %).

Also, the results confirm the general manageability of the side effects of these drugs. The AEs were predictable and manageable and did not deviate from the known toxicity profiles in terms of frequency or severity. Even though most of the patients experienced some type of AE, the rates of drug discontinuation due to AEs were identical and low, at 6.3 % in both arms. Diarrhoea was the predominant reason for drug discontinuation in the afatinib group, followed by fatigue and toxic skin eruptions. In the gefitinib arm, the most common causes of discontinuation were transaminase elevations and interstitial lung disease. Overall, LUX-Lung 7 confirms the benefits of irreversible ErbB blockade with afatinib compared to reversible EGFR inhibition with gefitinib in the treat-

ment of *EGFR*-mutation-positive NSCLC. These findings can be used to support treatment decisions between first-line TKIs in clinical practice.

### Update of LUX-Lung 8

Whereas LUX-Lung 7 compared afatinib and gefitinib in the first-line setting in patients with *EGFR*-positive adenocarcinomas, the global, randomised, open-label, phase III LUX-Lung 8 trial applied the afatinib *versus* erlotinib comparison to second-line patients with squamous-cell carcinomas, independent of mutation status. According to the primary analysis, significant improvements in PFS and OS have been achieved with afatinib over erlotinib [7].

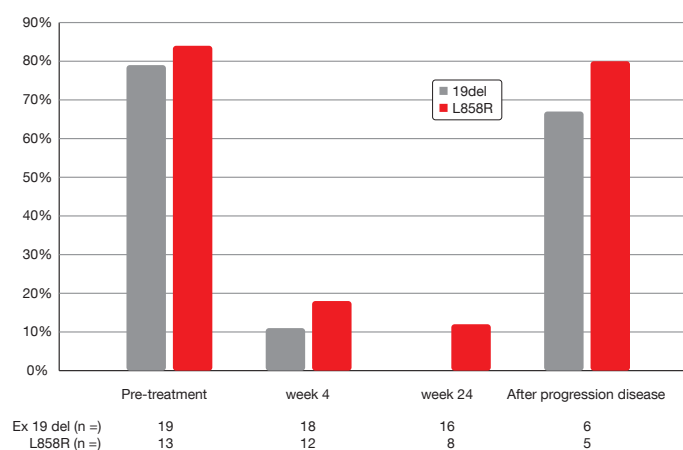
At the ESMO Asia Congress, the primary OS analysis after 632 deaths was reported, as well as updated PFS results and exploratory tumour genetic findings [8]. OS was significantly improved

with afatinib compared to erlotinib (median, 7.9 vs. 6.8 months; HR, 0.81;  $p = 0.0077$ ; **Figure 2**). The significant PFS advantage remained, with median results of 2.6 vs. 1.9 months (HR, 0.81;  $p = 0.0103$ ). Molecular aberrations occurred with incidences similar to those previously observed by The Cancer Genome Atlas Research Network. TP53, LRP1B, MLL2 SVs, SOX2, KLHL6, PIK3CA and MAP3K13 CNAs counted among the most frequent aberrations. The afatinib-related benefit was seen across all of the clinical and molecular subgroups. There was no predictive association between genetic alterations and OS or PFS. These data support afatinib as the TKI of choice in second-line treatment of patients with squamous-cell carcinoma of the lung.

### Biomarker findings for afatinib

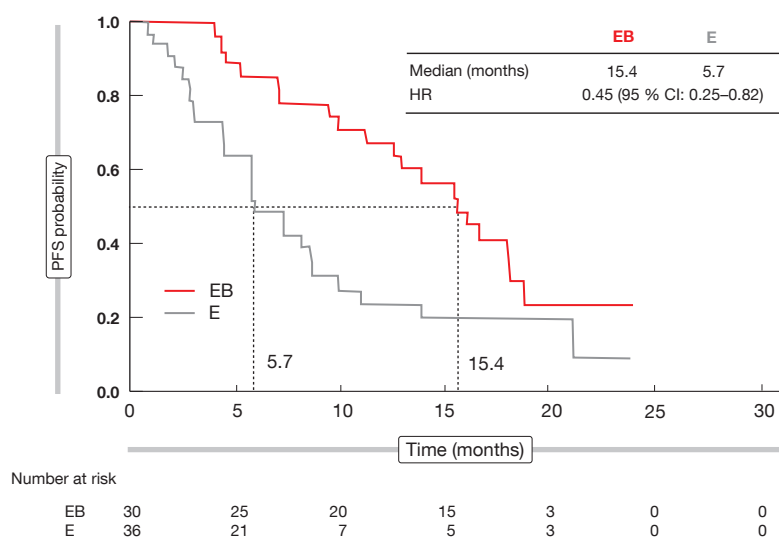
The efficacy of gefitinib and erlotinib monotherapies can be predicted by the early development of skin rash. To establish whether this relationship also applies to afatinib treatment, Bessho et al. retrospectively assessed 49 consecutive patients with *EGFR*-mutant NSCLC who received afatinib monotherapy between 2009 and 2015 [9]. Ten percent of the patients developed skin rash grade  $\geq 2$  within the first week. Multivariate analysis revealed a trend for increased responses with the occurrence of grade  $\geq 2$  early skin rash ( $p = 0.071$ ).

Studies hint at the usefulness of circulating free DNA (cfDNA) for the detection and monitoring of *EGFR* mutations. Iwama et al. provided prospective data for afatinib by evaluating tumour



**Figure 3:** Differences in the detection of active mutations in cfDNA before, during and after treatment with afatinib





**Figure 4:** Marked reduction in the risk of progression and death with erlotinib plus bevacizumab compared to erlotinib alone in patients with pleural and/or cardiac effusion

samples and blood samples from 35 afatinib-treated patients, with the aim of investigating the usefulness of non-invasive liquid biopsies [10]. Samples were taken before, during, and after treatment.

The treatment provided a response rate of 77.1 %. Disease control was achieved in 88.6 %, and median PFS had not been reached at the time of analysis. The detection rate of active mutations in cfDNA before the administration of afatinib was high, at 59.4 % for Scorpion-ARMS, 81.3 % for digital polymerase chain reaction, and 75.0 % for next-generation sequencing. After the start of treatment, the concentrations of L858R-positive alleles in cfDNA dropped sharply until week 4, and then stayed at low levels in the patients who did not progress. This was also true for the

concentrations of exon-19-deletion-positive alleles. Overall, active mutations were detected in cfDNA to a much greater extent before treatment and after progression than during treatment (Figure 3). The quantitative changes of active mutations thus reflected the clinical course of the disease.

### Addition of bevacizumab to erlotinib in specific circumstances

Anti-EGFR TKI monotherapy might not be sufficient in patients with certain clinical factors. A potential strategy to improve the efficacy of treatment is the combination with anti-vascular endothelial growth factor agents. The open-label, randomised, multicentre, phase II JO25567 trial demonstrated a

PFS advantage of erlotinib plus bevacizumab, as compared to erlotinib alone, in chemotherapy-naïve patients with non-squamous, *EGFR*-mutation-positive, stage IIIB/IV NSCLC [11]. For the entire cohort, median PFS was 16.0 versus 9.7 months with erlotinib plus bevacizumab and erlotinib monotherapy, respectively (HR, 0.54;  $p = 0.0015$ ).

A subgroup analysis of JO25567 that was presented at the ESMO Asia Congress showed consistent benefit for the addition of bevacizumab to erlotinib regardless of patient characteristics [12]. At the same time, some factors appeared to be associated with shorter PFS in the monotherapy arm. This was especially the case for baseline pleural and/or cardiac effusion (PCE). In patients with PCE, those who received erlotinib alone had a median PFS of only 5.7 months, compared to 15.4 months in the combination group (HR, 0.45; Figure 4). This difference was much smaller in patients without PCE (16.4 vs. 11.1 months, for erlotinib plus bevacizumab and erlotinib, respectively; HR, 0.62).

Objective response rates were approximately 70 % in the combination arm, regardless of whether PCE was present or not. On the other hand, in the monotherapy arm, patients with PCE had lower response rates (56 %) than those without (71 %). Progression of baseline PCE was more frequent in the monotherapy arm (30.6 %) than in the combination arm (16.7 %), which indicated improved control with the addition of bevacizumab. No new safety signals were observed, regardless of the presence of baseline PCE. ■

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## Disease progression on EGFR TKI therapy: what to do after erlotinib, gefitinib and afatinib?

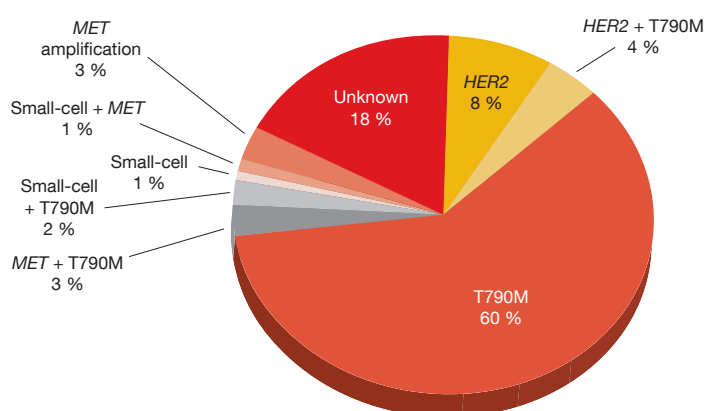
First-line treatment for patients with *EGFR*-mutation-positive NSCLC includes the first-generation reversible EGFR TKI inhibitors erlotinib and gefitinib, and the second-generation ErbB family blocker, afatinib. These drugs can elicit dramatic responses, but acquired resistance generally limits the successful long-term treatment. In the majority of patients, tumour progression eventually develops, due to resistance.

### T790M: culprit number 1

The most common mechanism of acquired resistance is the T790M mutation within exon 20 of the *EGFR* gene (**Figure 1**) [1]. Indolent slow tumour growth typically occurs when this mutation emerges [2]. "Repeated imaging may be necessary to identify progression," explained Pasi A. Jänne, MD, PhD, Lowe Center for Thoracic Oncology, Dana Farber Cancer Institute, Boston, USA, during a symposium at the ESMO Asia Congress.

T790M works through an unusual resistance mechanism, in that it changes the affinity of the EGFR receptor for its natural substrate, ATP. While drugs like gefitinib and erlotinib are competitive inhibitors that outcompete the ATP binding at the binding site, the receptor shows greater affinity for ATP in the presence of this mutation. The original publication that described the T790M mutation in 2005 suggested the need for the development of covalent EGFR inhibitors as a potential solution with which to overcome the competitive advantage of T790M [3]. This led to the evaluation of covalent EGFR inhibitors. Two randomised phase III clinical trials assessed afatinib and dacomitinib in patients who had developed resistance to gefitinib and erlotinib [4, 5]. "However, the beneficial effects in terms of response rates, PFS or OS, as compared to placebo, were negligible" Dr. Jänne said.

Other types of aberrations can also mediate resistance, such as *MET* amplification or small-cell transformation. Small-cell transformation has com-



**Figure 1:** Relative frequencies of mechanisms of acquired resistance in *EGFR*-mutation-positive tumours

pletely different effects from the T790M mutation, and it gives rise to rapid progression. These tumours can show the appearance of small-cell lung cancer (SCLC) and respond to SCLC treatments.

### General principles of management

As Dr. Jänne explained, the first question that needs to be answered when progression occurs on EGFR TKI therapy is whether this progression is clinically significant in the individual patient. Tumour growth according to RECIST does not always necessitate a change of strategy, particularly if the patient is tolerating the treatment well. "Many patients receive post-progression TKI therapy." This especially applies to patients experiencing longer PFS, a better response, and better performance status, according to the ASPIRATION trial [6].

One of the aspects that has been gaining attention is the use of local therapies, such as stereotactic radiation for brain metastases, isolated lung metastases, or bone metastases, while systemic anti-EGFR treatment is maintained. "This can be an alternative to discontinuation, if the patient shows only a single site of growth," Dr. Jänne noted. The data provided by Weickhardt et al. suggested potential benefits by such a combined ap-

proach, especially in patients with CNS metastases as the first site of progression [7]. However, patients need to be selected carefully. The treatment decisions depend on the pattern of progression and the availability of local therapies. Finally, it should be established whether re-biopsy is feasible and whether a switch to chemotherapy should be considered.

Continuation of EGFR TKI treatment after the switch to chemotherapy used to be very common in clinical practice. Practice-changing results were generated by the IMPRESS trial, however [8]. Here, continuation of gefitinib together with chemotherapy did not provide any benefit compared to chemotherapy alone for PFS or response.

### A TKI penetrating the brain: osimertinib

Progression is frequently observed in the same or similar locations where the initial tumour was identified. Sometimes it is confined to the CNS, with brain metastases or leptomeningeal disease emerging. "Many of the current EGFR inhibitors show poor penetration into the CNS, which poses problems in clinical practice," Dr. Jänne said.

An exception to this is the third-generation EGFR TKI osimertinib (AZD9291) that has been developed to inhibit the T790M mutation rather than

any of the other types of resistance mechanisms. It effectively penetrates the CNS. Osimertinib is approved for the treatment of T790M-mutation-positive NSCLC in the United States and Europe.

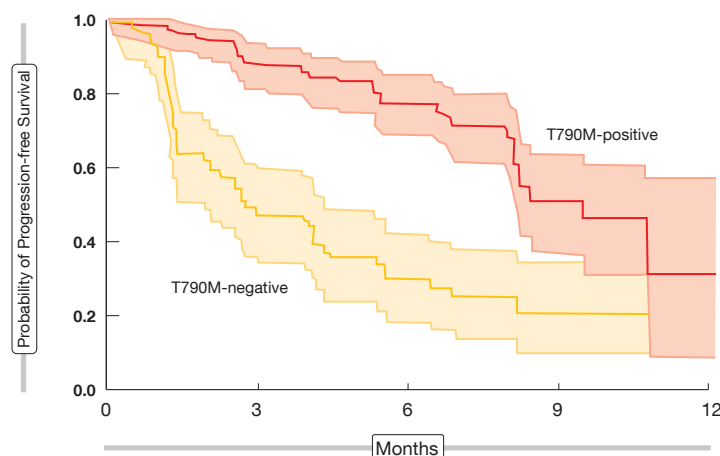
In the trial by Lee et al., a significant proportion of patients with leptomeningeal disease experienced responses to osimertinib treatment that were accompanied by significant clinical improvement [9]. Changes in the EGFR mutant copy number were obtained in the cerebrospinal fluid. A phase I study demonstrated greater efficacy of osimertinib in patients harbouring the T790M mutation than in those without it; the Kaplan-Meier plot showed instant separation of the PFS curves between these two populations (**Figure 2**) [10]. The AURA3 phase III trial is currently testing osimertinib compared to platinum-based doublet chemotherapy for advanced or metastatic T790M-mutation-positive NSCLC.

### BI 1482694

Another third-generation *EGFR*-mutant-specific drug is BI 1482694, which is active against mutant *EGFR* isoforms including T790M, while sparing wild-type *EGFR*. An open-label, multicentre phase I/II trial conducted in Korean patients assessed the safety and tolerability of BI 1482694, as well as its clinical activity at the recommended phase II dose [11]. Lee et al. presented findings at the maximum tolerated dose and at the recommended phase II dose of 800 mg once daily, in 76 patients with T790M-positive NSCLC who had previously been treated with an *EGFR* TKI [12].

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**Figure 2:** Greater PFS benefit of osimertinib in T790M-mutation-positive patients than in the T790M-mutation-negative cohort

In the 69 patients who were evaluable for response by independent assessment, the objective response rate was 62 %. Responses were observed early on. Eighty-four percent of confirmed objective responses were achieved by week 6. Median duration of response had not yet been reached at the time of the analysis. The ORR was similar whether or not the last treatment prior to study entry had been an *EGFR* TKI or chemotherapy. Disease control was obtained in 91 %. The most common treatment-related AEs included mild-to-moderate gastrointestinal symptoms (e. g., diarrhoea, nausea) and dermatological toxicity (e. g., rash, pruritus). There was no obvious effect on the QTc interval or glucose metabolism at the dose of 800 mg daily.

The ELUXA programme will assess the efficacy and safety of BI 1482694 in various settings of *EGFR*-mutated NSCLC. Findings in the T790M-positive patients are currently being generated in the

phase II ELUXA 1 trial. Further third-generation *EGFR* TKIs, such as rocletinib, ASP8273 and EGF816, are under clinical evaluation.

### The future of *EGFR* inhibition

According to Dr. Jänne, physicians are finally in a position to begin to answer the question of the best sequence to use for *EGFR* inhibitors. Even allowing for the limited number of drugs available to date, there is the choice between starting a patient on a first-generation or second-generation *EGFR* inhibitor, followed by a third-generation inhibitor, or using third-generation inhibitors from the very start of the treatment. “The latter is rapidly becoming a more interesting option, even though more data are required to find out if this is a suitable approach,” Dr. Jänne explained. Initial data from the phase I clinical trial conducted with osimertinib indicates that first-line results might be superior to those that can be ex-



pected with first-generation EGFR inhibitors [13]. The study contained a cohort of EGFR-TKI-naïve individuals; these patients achieved an objective response rate of 75 %, and their median PFS had not yet been reached at the time of the analysis. “Although this was only a small cohort, the results are certainly encouraging,” Dr. Jänne emphasised. Also, the ongoing FLAURA trial, which is comparing osimertinib with gefitinib or erlo-

tinib, will provide further insights on the use of this class of agents as an initial treatment.

Long-term success will ultimately require combination therapies, as Dr. Jänne pointed out. Combination studies were not feasible with older EGFR inhibitors due to overlapping toxicities, but they can be conducted with these new drugs. Various combination trials are ongoing. Common strategies include MEK

and MET inhibition combinations as well as immunotherapy combinations. “The opportunity for all of us lies in figuring out which combination therapy to use and to decide whether this should be the initial treatment, an option after first-generation drugs, or the therapy of choice after the failure of successive EGFR TKI treatment,” Dr. Jänne summarised. “Preclinical trials will hopefully be able to provide answers to this.” ■

## Risks and chances in patients with oligometastatic disease

Against the background of improved systemic therapies, there are rising expectations with regard to the potential cure of NSCLC patients who have a limited number of haematogeneous metastases. “Most studies define oligometastasis as one to three, or one to five lesions,” explained Suresh Senan, MRCP, FRCR, PhD, VU University Medical Centre, Amsterdam, The Netherlands [1]. Depending on the clinical scenario, there are synchronous (detection at the time of diagnosis of the primary tumour) and metachronous (development after treatment of the primary tumour) oligometastases. As Dr. Senan pointed out, the interval that allows for differentiation between these two is not standardised, but a time span of 6–12 months is commonly used.

The term of oligorecurrence describes oligometastasis in the setting of a controlled primary tumour. ‘Oligoprogression’, on the other hand, refers to progression of a limited number of known metastatic lesions, while all other metastases are controlled with systemic therapy.

### Identification of prognostic factors

Ablative therapies include surgical resection, stereotactic radiotherapy, and radiofrequency ablation. However, there is a general lack of evidence with

**TABLE**  
**Risk stratification after treatment of oligometastatic NSCLC**

Low risk: metachronous metastases (5-year OS, 49 %)
Intermediate risk: synchronous metastases and N0 disease (5-year OS, 36 %)
High risk: synchronous metastases and N1/N2 disease (5-year OS, 14 %)

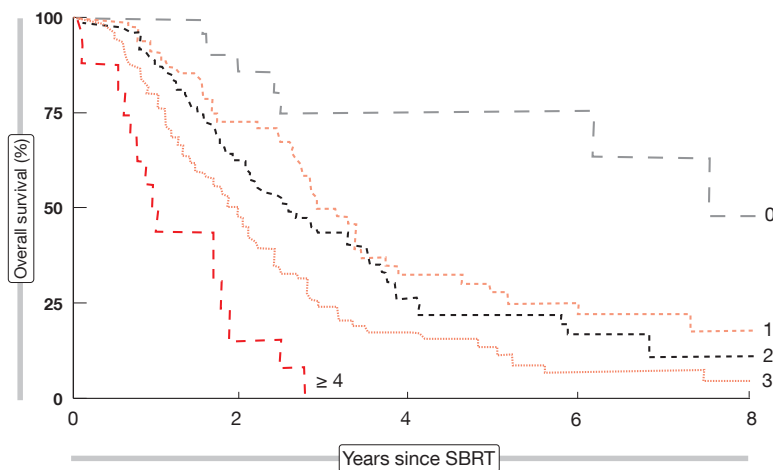
respect to these treatments, and data can be unreliable due to several types of bias, including selection bias or immortal time bias. “The only high-level evidence according to which aggressive treatment of metastases improves survival has been obtained in patients with brain metastases,” reported Dr. Senan. A trial published in 1990 showed that addition of surgical resection to whole-brain radiotherapy (WBRT) in patients with a single brain lesion improved median OS from 15 to 40 weeks [2]. According to another study, in patients with up to three CNS metastases, radiosurgery in addition to WBRT provided an OS benefit (6.5 months vs. 4.9 months with WBRT alone) [3].

A meta-analysis of 757 NSCLC patients with one to five synchronous or metachronous metastases investigated factors for good prognosis after treatment [4]. “These were generally younger patients with a good performance status,” said Dr. Senan. Importantly, after exclusion of metastatic disease, two thirds had early-stage intra-thoracic disease (IA–IIB rather than stage III). Thus, they were hardly representative of

the average NSCLC patient population. Median OS was favourable at 26 months, and the 5-year OS rate was 30 %. The researchers identified the following predictors for improved OS: metachronous *versus* synchronous metastases ( $p < 0.001$ ), N stage ( $p = 0.002$ ), and adenocarcinoma histology ( $p = 0.036$ ). Three risk groups were defined through recursive partitioning analysis (Table).

### Irradiation techniques

Stereotactic body radiotherapy (SBRT) is a technique for delivering high-dose external beam radiotherapy to an extra-cranial target with a high degree of accuracy. The largest series of patients treated with SBRT for oligometastatic disease included 321 cancer patients from Denmark [5]. Favourable prognostic factors were performance status of 0–1, solitary metastasis, diameter of metastatic lesions  $< 30$  mm, metachronous metastases, and pre-SBRT chemotherapy. OS after SBRT declined considerably when four or more unfavourable factors were present (Figure).



**Figure:** Survival after SBRT according to the number of unfavourable prognostic factors

Stereotactic radiosurgery (SRS) is an accepted treatment modality for patients with one to four brain lesions that measure 4 cm or less in diameter [6]. SRS alone or in combination with surgical resection or WBRT can lead to good local control in patients with brain metastases. The role of WBRT is currently under debate. A pooled analysis from three phase III trials in a total of 264 patients showed that in patients aged 50 years or younger, WBRT can be omitted without any detrimental effects [7]. SRS as a stand-alone therapy was sufficient in this group. Similarly, there was an age effect for out-of-field brain metastases (distant brain failure): younger patients experienced no increased risk of out-of-field cerebral relapse with SRS alone, while the addition of WBRT reduced the risk for those over 50 years of age. “Part of the debate relates to whether it is necessary to irradiate an elderly brain,” said Dr. Senan. “Many of us have these patients

undergo MRI follow-up every three months and treat subsequent metastases when they appear.”

#### Patients with *EGFR* or *ALK* aberrations

Given the wealth of new treatment options, a question that needs to be answered is whether ablative radiotherapy complements targeted agents and immunotherapies. In TKI-treated patients, irradiation is obviously not urgently required after the detection of asymptomatic metastatic brain lesions. “We can wait for systemic therapy to start working,” Dr. Senan explained. Once progression sets in, there is a reasonable chance of achieving local control. Alectinib-treated patients with *ALK*-rearranged, crizotinib-refractory NSCLC and baseline CNS metastases (measurable or non-measurable) without prior radiation showed a complete CNS response rate of 43 % in a global phase II trial [8].

Those with measurable baseline lesions attained a CNS ORR of 57 %. According to the ESMO guidelines from 2014, oligometastatic progression during targeted treatment can be ablated with local treatment (such as surgery or radiotherapy), while TKI therapy is continued or resumed [6]. Before proceeding with local therapy, a full evaluation of the extent of the disease, including CNS imaging, is recommended.

“At present, we prefer to go for systemic treatment in patients without a high symptom burden,” Dr. Senan reported. “If they progress, on-demand stereotactic radiotherapy is used.” Local treatment that is limited to specific lesions, which are suspected to cause the patient’s symptoms, are an option while systemic therapy continues.

#### Radiation plus immunotherapy: boosting the local immune system

Yet another challenge arises in the context of immunotherapy, because radiotherapy has been shown to have both immunomodulatory and immunosuppressive effects. Irradiation induces tumour cell apoptosis, release of tumour antigens, and expression of immunogenic cell death receptors, like calreticulin and HMGB-1, as well as up-regulation of immunogenic cell-surface markers, such as MHC-1 [9]. Homing of immune cells and antigen presentation are improved. On the other hand, PD-L1 expression also increases, and Langerhans cells in the skin migrate to lymph sites, which results in up-regulation of regulatory T cells [10].

One of the peculiarities of radiotherapy that has attracted attention is

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the relatively uncommon phenomenon of abscopal effects. This term refers to regression of non-irradiated metastatic lesions that are distant from an irradiated tumour site. These responses are believed to be immune mediated [11]. “The idea is that radiotherapy combined with immunotherapy might increase the abscopal effect,” Dr. Senan pointed out [12]. “The treatment could thus be given a kick-start, and prediction of response might be improved.” Issues such as optimal sequencing and radiation dosing remain unclear, however.

### Current dilemmas

To date, safety data for sequencing or combining irradiation with new agents are lacking. This is all the more relevant as drugs are being approved at a rapid pace. “We are now much more careful regarding the choice of radiation techniques,” Dr. Senan emphasised. When complications occur, such as bowel perforation in a TKI-treated patient, it is difficult to identify the actual cause. Moreover, it happens that recommendations are sometimes contradictory within the multidisciplinary team. “The pulmonol-

ogist might instruct the patients to continue their systemic treatment, while the radiation oncologist may ask them to stop it until the radiotherapy is completed.”

Overall, as high-quality evidence still needs to be generated, caution is required regarding the multimodal approach. “Potential benefits must be balanced against the risks of unexpected morbidity and mortality,” Dr. Senan summarised. ■

**Source:** Educational Session: Optimal therapy for earlier stages of NSCLC, 21<sup>st</sup> December, 2015

## Immunotherapy: anti-tumour activity despite extensive pretreatment

The anti-PD-1-antibodies pembrolizumab and nivolumab have been shown to be active in lung cancer. Pembrolizumab is a high-affinity, humanised, monoclonal IgG4κ antibody against PD-1 that prevents the interaction of the receptor with PD-L1 and PD-L2. The KEYNOTE-001 trial demonstrated significant anti-tumour activity of pembrolizumab in advanced NSCLC, with improved outcomes in terms of PD-L1 Tumor Proportion Scores (TPS)  $\geq 50\%$  [1]. The TPS reflects the expression of PD-L1 on the tumour. The  $\geq 50\%$  cut-off was determined using independent training and validation datasets from KEYNOTE-001.

Pembrolizumab is approved in the US for treatment of patients with advanced, PD-L1-positive NSCLC that has progressed after platinum-containing chemotherapy and appropriate TKI therapy for *EGFR* or *ALK* genomic aberrations.

### KEYNOTE-010

Additional data are provided by the randomised phase II/III KEYNOTE-010 trial, which included patients with PD-L1-positive advanced NSCLC and disease progression after at least one

line of chemotherapy [2]. Two doses of pembrolizumab (2 mg/kg every 3 weeks, or 10 mg/kg every 3 weeks, for 24 months) were compared with docetaxel (75 mg/m<sup>2</sup> every 3 weeks, per local guidelines). Patients had to be PD-L1 positive. A TPS of  $\geq 1\%$  was one of the inclusion criteria, and PD-L1 status was a stratification factor (i.e., TPS  $\geq 50\%$  vs. 1 %–49 %). The following endpoints were assessed separately for the TPS  $\geq 50\%$  and TPS  $\geq 1\%$  groups: PFS and OS (co-primary), objective response rate (ORR), duration of response, and safety (secondary).

The screening included 2,699 patients, 1,475 of whom were PD-L1 positive with TPS  $\geq 1\%$ . Initially, both archival biopsies and new tissue samples were allowed for the tumour analysis, although after an amendment, new tumour samples had to be used unless the risk of a biopsy was considered too high. Overall, 456 out of 1,034 randomised patients participated in the trial based on archival samples. Approximately 20 % in each arm had squamous-cell carcinoma. *EGFR* mutations were found in 8 %, 9 % and 8 % of patients treated with pembrolizumab 2 mg/kg, 10 mg/kg, and docetaxel, respectively. The analysis revealed a PD-L1 TPS of  $\geq 50\%$

and 1 %–49 % in approximately 40 % and 60 % of the patients, respectively, across the treatment arms. Twenty percent to 30 % of the patients received the study treatment as third line or later lines.

### Outcome improvements in patients with TPS $\geq 1\%$

In the TPS  $\geq 50\%$  group, pembrolizumab treatment at both doses gave rise to highly significant OS benefits compared to docetaxel chemotherapy (HR, 0.54, 0.50 with 2 mg/kg, 10 mg/kg, respectively;  $p = 0.0002$ ,  $p < 0.0001$ , respectively). The median survival rates obtained with pembrolizumab were nearly doubled compared to docetaxel. The results for the TPS  $\geq 1\%$  group were of particular interest, as these represented the majority of the patients. Again, the two pembrolizumab doses showed similar activities (**Figure**), with the mortality risk reduced by 29 % and 39 %, respectively, compared to docetaxel ( $p = 0.0008$ ,  $p < 0.0001$ , respectively). The OS benefit emerged early on. All of the subgroups (i.e., sex, age, ECOG performance status, tumour sampling [archival vs. new], histology, *EGFR* status) benefited from the pem-

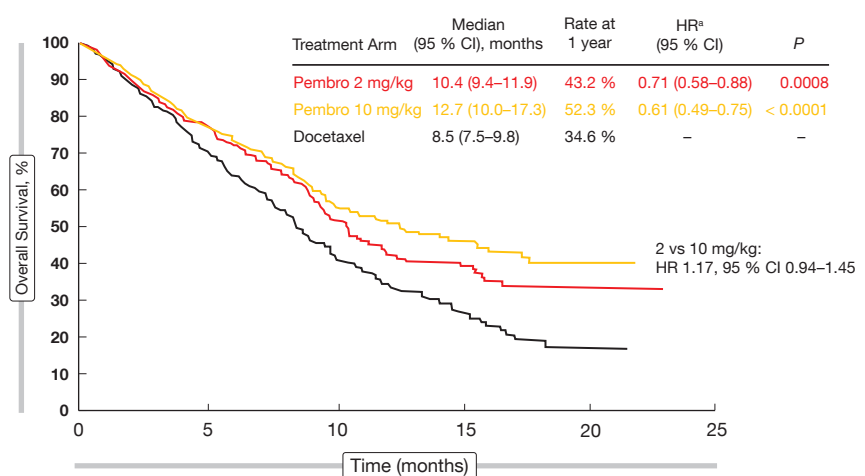
brolizumab treatment. This advantage of pembrolizumab also applied to both of the TPS groups ( $\geq 50\%$  vs.  $1\%$ – $49\%$ ), which is relevant for treatment decisions.

For PFS, the analysis also favoured pembrolizumab treatment to a significant extent in both of the TPS groups. For the TPS  $\geq 50\%$  group, the HRs were 0.59 for both pembrolizumab doses compared to docetaxel ( $p = 0.0001$ ,  $p < 0.0001$ , respectively). For the TPS  $\geq 1\%$  group, the HRs were 0.88 and 0.79, respectively ( $p = 0.07$ ,  $p = 0.004$ , respectively). The response rates were highly significantly improved in the TPS  $\geq 50\%$  group (30 %, 29 % vs. 8 %;  $p < 0.0001$  for both comparisons), as well as in the TPS  $\geq 1\%$  group (18 % for both pembrolizumab doses vs. 9 % for docetaxel;  $p = 0.0005$ ,  $p = 0.0002$ , respectively). Also, the duration of these responses was considerably longer with both pembrolizumab doses than with docetaxel, irrespective of TPS.

### Pembrolizumab: a new standard of care

Pembrolizumab treatment was well tolerated, with markedly lower rates of high-grade toxicity compared to docetaxel. Approximately half as many patients in the pembrolizumab arms *versus* the docetaxel arm discontinued treatment due to AEs. Immune-related events occurred with a maximum incidence of 8 %. The main immune-mediated AEs were hypothyroidism and hyperthyroidism, and most of these were rated as low grade. From 2 % to 3 % of the patients treated with the two pembrolizumab doses developed pneumonitis, and although this AE also emerged in the docetaxel-treated arm, it did so less frequently. Again, pneumonitis was low-grade in the majority of cases.

Overall, the data obtained from the KEYNOTE-010 trial validate the use of the PD-L1-positivity selection in advanced NSCLC. They support the treatment schedule of pembrolizumab 2 mg/kg every 3 weeks that is currently approved in the US for patients with advanced NSCLC. Moreover, these findings support pembrolizumab as one new standard of care for patients with advanced NSCLC that show disease progression on platinum-based chemotherapy.



**Figure:** Overall survival with pembrolizumab at two doses vs. docetaxel in the population with TPS  $\geq 1\%$  (KEYNOTE-010)

### Nivolumab in non-squamous NSCLC: CheckMate 057

The fully human IgG4 PD-1 immune checkpoint inhibitory antibody nivolumab has been approved in the US for treatment of patients with metastatic NSCLC whose disease has progressed on or after platinum-based doublet chemotherapy and after anti-EGFR or anti-ALK TKI therapies. In Europe, the approval extends to patients with locally advanced or metastatic squamous-cell NSCLC whose disease has progressed on or after prior chemotherapy.

The randomised phase III CheckMate 057 trial investigated nivolumab *versus* docetaxel in pre-treated patients with advanced non-squamous-cell NSCLC (independent of PD-L1 status). Docetaxel served as the comparator because it is a standard second-line treatment in this setting. This treatment can be expected to give rise to response rates of 9.0 % to 14.5 %, and median OS of 8.0 months to 10.4 months.

In CheckMate 057, the patients were randomised to either nivolumab 3 mg/kg every 2 weeks or docetaxel 75 mg/m<sup>2</sup> every 3 weeks. Prior maintenance therapy was allowed, as well as prior TKI treatment for patients with known *EGFR* mutation or *ALK* translocation. The primary endpoint was OS, while the secondary endpoints included ORR, PFS, safety, efficacy according to PD-L1 expression, and patient-reported outcomes. Tumour tissue was available for PD-L1 expression analysis in approximately 80 % of the patients, and about

half of these showed as PD-L1 positive. At the ESMO Asia Congress, the 18-month analysis of the CheckMate 057 trial was presented, along with the subgroup analyses and patient-reported outcomes.

### Correlation between PD-L1 status and benefit

According to the primary analysis, OS was significantly improved by nivolumab (12.2 vs. 9.4 months with nivolumab and docetaxel, respectively;  $p = 0.0009$ ), which provided a reduction in the mortality risk of 28 % [3]. Even though the Kaplan-Meier curves crossed in the beginning, the analysis clearly showed consistent benefit of the immunotherapy over the longer term [4]. At 18 months, OS rates were 39 % vs. 23 %, respectively. Also, the primary analysis demonstrated improvements in ORR (19 % vs. 12 %;  $p = 0.0246$ ) and duration of response (17.2 vs. 5.6 months). Superior responses to nivolumab were also observed across almost all of the subgroups. This benefit stood out in the group of former and current smokers (ORR: 22 % vs. 11 %). Conversely, the ORR for nivolumab was slightly lower compared to docetaxel in the group of patients with positive *EGFR* mutation status (11 % vs. 16 %).

An exploratory analysis established a potential correlation between PD-L1 expression status and efficacy of nivolumab. Indeed, whereas survival appeared to be comparable in the two treatment arms in the PD-L1-negative



**TABLE 1**  
**CheckMate 057: Response to nivolumab and docetaxel according to tumour PD-L1 expression**

PD-L1 expression level, %	ORR, %		Median duration of response, months	
	Nivolumab	Docetaxel	Nivolumab	Docetaxel
≥ 1	31	12	16.0	5.6
≥ 5	36	13	16.0	5.6
≥ 10	37	13	16.0	5.6
< 1	9	15	18.3	5.6
< 5	10	14	18.3	5.6
< 10	11	14	18.3	5.6
Not quantifiable	13	9	7.3	6.6

subgroup, nivolumab-treated patients fared better than those who received docetaxel when they were PD-L1 positive. Moreover, there was a correlation between PD-L1 expression status and ORR, again favouring patients with PD-L1-positive tumours (**Table 1**). Duration of response, on the other hand, was not affected by PD-L1 status.

### Patient-reported outcomes in CheckMate 057

Symptom burden was assessed using a pre-specified Lung Cancer Symptom Scale questionnaire, which covers the most important lung-cancer-related symptoms (e.g., fatigue, dyspnoea, pain, haemoptysis, cough, anorexia). The pre-defined secondary endpoint was symptom improvement rate at week 12. For this outcome, the results were comparable between the two arms, although the nivolumab therapy appeared to do better, and provided symptom stabilisation over time.

With respect to tolerability, the analysis showed that the administration of nivolumab resulted in substantially fewer AEs. This was particularly true for grade 3/4 treatment-related AEs, severe AEs, and events that led to discontinua-

tion. However, specific immune-related toxicity, which has been described for all anti-PD-1 and anti-PD-L1 antibodies, occurred in some patients. Overall, the safety profile of nivolumab was favourable compared to that of docetaxel, and consistent with prior studies.

The authors concluded that in CheckMate 057, nivolumab continues to demonstrate superior OS versus docetaxel in pre-treated patients with advanced non-squamous NSCLC. The magnitude of benefit was greater among the PD-L1 expressors compared to the non-expressors, although there were clinical benefits in both groups.

### Durvalumab plus tremelimumab

Dual immune checkpoint blockade with anti-CTLA-4 and anti-PD-1 antibodies is an established option in the treatment of melanoma. These two approaches enhance T-cell anti-tumour activity through different but complementary mechanisms. The notable effects of this strategy include particularly pronounced depth of response, which is known to correlate with improved long-term benefit. Promising activity of ipilimumab plus nivolumab in lung cancer

was already obtained in the CheckMate 012 trial; here, patients with advanced NSCLC received the two antibodies in the first-line setting [5]. The combination gave rise to deep and durable responses.

Another potentially useful dyad is the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab. A non-randomised, open-label, phase Ib dose-escalation and dose-expansion trial assessed the safety and anti-tumour activity of this combination in patients with advanced NSCLC [6]. Multiple dose combinations were tested: durvalumab was administered at 3 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg, every 2 or 4 weeks for 26 or 13 doses, respectively; and tremelimumab was administered at 1 mg/kg, 3 mg/kg or 10 mg/kg, every 4 weeks for six doses, followed by three additional doses every 12 weeks. These treatments continued for 1 year or until disease progression. PD-L1 expression was evaluated by immunohistochemistry.

As of June 1, 2015, 102 patients have been treated in the dose-escalation phase across five centres in the US. The majority have non-squamous histology, and most are former or current smokers. More than half of these patients had already received two or three lines of treatment.

### Durable responses

The grade-3/4 AE rate was 42 % in the total study population. Immune-related AEs occurred as expected, with gastrointestinal toxicity arising most frequently. Diarrhoea was observed in 32 % of the patients, and 11 % experienced grade ≥ 3 symptoms. Rash and pruritus emerged as well, but were restricted to grades 1 and 2. The increased tremelimumab dosing reduced the tolerability of the treatment. Pneumonitis, for instance, did not occur at a dose of

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1 mg/kg, but showed considerable incidence at 3 mg/kg and 10 mg/kg. The majority of AEs in the tremelimumab 1 mg/kg cohort were manageable and reversible using standard treatment guidelines.

Fortunately, the tremelimumab dose of 1 mg/kg was sufficient to achieve significant anti-tumour activity. In the tremelimumab 1 mg/kg cohort, the ORR was 28 % in the total population and 44 % in the second-line patients. Responses were seen independent of PD-L1 expression, whereby patients responded even if they showed no PD-L1 expression at all. Sixty-six percent had ongoing responses at the time of the data cut-off, which indicates the durability of this treatment activity.

**TABLE 2**  
**Open and enrolling phase III trials investigating durvalumab plus tremelimumab in NSCLC and other indications**

ARCTIC: 3 <sup>rd</sup> line and later lines NSCLC (NCT02352948)
KESTREL: 1 <sup>st</sup> line SCCHN (NCT02551159)
MYSTIC: 1 <sup>st</sup> line NSCLC (NCT02453282)
NEPTUNE: 1 <sup>st</sup> line NSCLC (NCT02542293)
EAGLE: 2 <sup>nd</sup> line SCCHN (NCT02369874)
DANUBE: 1 <sup>st</sup> line metastatic bladder cancer (NCT02516241)
SCCHN: Squamous-cell carcinoma of the head and neck

Compared to monotherapy data presented at the ASCO Congress 2015 that were obtained with durvalumab alone [7], the durvalumab plus tremelimumab combination gave rise to markedly improved ORRs. The combined treatment of durvalumab 20 mg/

kg every 4 weeks with tremelimumab 1 mg/kg every 4 weeks has been selected for assessment in the phase III setting. Several phase III trials with this combination in NSCLC and other indications are open and enrolling (**Table 2**). ■

**Interview:** Martin Reck, MD, PhD, Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Germany

## “PD-L1 expression is a nightmare in terms of complexity”



**Martin Reck, MD, PhD, Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Germany**

**Immunotherapies offer advantages in unselected patients. However, the implementation of biomarkers would be highly welcome. One of the reasons for this would be containment of the financial strain on health systems, as physicians could then exclude patients who are unlikely to benefit from treatment. Where are we today regarding biomarker development?**

There are two issues that are tied to the

topic of biomarkers in immunotherapies. First, all attempts to define biomarkers have focused primarily on response as a marker of efficacy. We have to be aware, however, that immunotherapies are not targeted therapies, and fast tumor shrinkage is not necessarily observed with this kind of treatment. The efficacy of an immunotherapy is defined by long-lasting tumor stabilization. We have to question whether response rates are the appropriate endpoint here.

The second issue is the necessity to define the purpose of biomarker development in immunotherapies. There are two options: Biomarkers can identify patients who derive benefit from a specific treatment, or they can exclude those patients who are unlikely to benefit. This is something that needs to be defined. Currently, both strategies are being explored.

**What kind of evidence is available at present?**

Based on analyses from the CheckMate trials, it can be said that neither patient age nor performance status have any

impact on the efficacy of anti-PD-1 antibodies. The same is true for tumor histology. We have seen long-lasting responses to anti-PD-1 antibodies and anti-PD-L1 antibodies in patients with both squamous and non-squamous tumors. One factor of interest is smoking. The CheckMate trials have revealed superior response rates in the group of smokers or former smokers [1, 2]. This signal was found with other anti-PD-1/PD-L1 agents as well; for pembrolizumab, increased benefit was also apparent in terms of PFS and OS [3]. Smoking is known to induce a chronic inflammatory response in pulmonary tissue. Moreover, lung cancers of smokers have 10 times as many mutations as those of non-smokers. A high mutational load contributes to the immunogenicity of a tumor and might be correlated to the efficacy of immunotherapies. Data from Rizvi demonstrated an interesting association between the mutational load and the efficacy of pembrolizumab treatment in patients with pre-treated NSCLC [4]. This applied to response rates and PFS. A molecular smoking signature was

**TABLE**  
**Challenges surrounding the development of PD-L1 expression as a biomarker**

Biology	Technical: assays	Logistics: tissue
Inter-tumoral and intra-tumoral heterogeneity	Epitope stability	Interval between tissue and treatment (archived <i>versus</i> fresh material)
Inducible and dynamic (IFN, post-treatment)	Distribution (patchy <i>versus</i> diffuse)	Primary <i>versus</i> metastatic disease
Cell type (immune cell <i>versus</i> tumor cell <i>versus</i> both)	Different antibodies and platforms	Some circumstances are not amenable to obtaining any tissue
Location (membrane <i>versus</i> cytoplasm)	Different thresholds for expression	Certain biopsy methods result in poor tissue quality/quantity
	Inter-observer readability	

developed that correlated with these endpoints. Perhaps an inflammatory signature will be relevant in the future. Interesting data obtained with the anti-PD-L1 antibody durvalumab have suggested that there is a group of tumors that is driven by inflammation and that is highly susceptible to immunotherapy [5]. Disappointingly, no blood-based markers with any predictive power for the use of anti-PD-1/PD-L1 antibodies have been identified so far.

#### What do we know about tumors with low mutational burden; for example, those with activating *EGFR* mutations?

These data are limited and explorative. However, some signals were derived from the CheckMate 057 trial. It appears that the efficacy of nivolumab compared to docetaxel is slightly inferior in the group of patients with positive *EGFR* mutation status [6, 7]. Similar signals were observed for other anti-PD-1/PD-L1 antibodies, like atezolizumab [8, 9] and pembrolizumab [10, 11].

#### PD-L1 expression has been the main focus of biomarker research for quite some time. How would you rate the relevance of this marker?

PD-L1 expression is independent of any other molecular marker. A clear correla-

tion across all anti-PD-1/PD-L1 antibodies has been found between PD-L1 expression status and response, as well as PFS and OS, even in the first-line setting. However, we must be aware that PD-L1-negative patients can have 1-year OS rates of 70 %.

PD-L1 is not an easy-to-handle marker. Actually, it is a nightmare in terms of complexity, with a number of issues regarding biology, assays, and logistics (Table). In practice, different assays are used for measurement, and with different definitions of PD-L1 positivity added in, the story of PD-L1 assessment becomes very complicated. At the moment, at least four different test methods are in use. This will not be practical if we are going to apply immunotherapy in the clinic.

Undoubtedly, further development and harmonisation of PD-L1 assessment is urgently needed. An ongoing global initiative, which was put together by drug manufacturers, companies that provide testing systems, scientific societies, and regulatory authorities, is aimed at providing practical guidance on the use of PD-L1 expression.

#### What about additional markers?

For PD-L2, high concordance with PD-L1 expression has been demonstrated,

and there is an association with the response to anti-PD-1 antibodies after adjustment for PD-L1 expression [12]. PD-L2 is highly expressed in tumors, in the endothelial and stromal cells of NSCLC, but minimally expressed in normal tissue. Furthermore, infiltration of CD8+ cells into the 'invasive margin' of tumors is of interest. Tumor response to anti-PD-1/PD-L1 antibodies was shown to correlate with the density of pre-existing D8+ cells [13].

#### Apart from *EGFR* mutation, which molecular targets will gain importance in the future?

Data are coming up with respect to new targeted therapies; for example, for *BRAF* inhibitors. *BRAF* mutation occurs in 2 % to 3 % of our lung-cancer patients. We have already seen very interesting data in this area. A trial on the combination of a *MEK* inhibitor and a *BRAF* inhibitor in patients with *BRAF* mutation is ongoing. I believe that a targeted option will become available for this group of patients. Another druggable target is *RET* translocation. To my mind, the future will not be driven primarily by identification of molecular targets, but rather by identification of resistance mechanisms after first-line targeted therapies, and the development of adequate

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treatments in the refractory third-line situation.

We are at a stage now where we can talk about the whole treatment. The patients will not be cured, but we can offer them a long period of disease-free survival or stable disease. The sequence of therapies will become very important, which also applies to the possibility of offering the patient another active compound after progression. This is already a reality in *EGFR*-mutated patients; after progression, treatment can be continued with a third-generation

agent. In the future, fourth-generation or fifth-generation TKIs might become available.

#### What are the greatest challenges at present in the treatment of lung-cancer patients from a practical point of view?

One of the greatest challenges is the dynamics of drug development. A great number of new compounds is available, and the treatment has become very complex. The greatest challenge, however, is the accessibility of the tumor tis-

sue. In lung-cancer patients, it is sometimes extremely difficult to procure sufficient material for all of the required molecular or translational analyses. The question of whether we can develop molecular tests that work with a limited amount of tissue will soon be of paramount importance. Another challenge, of course, is the pharmaco-economic impact of the new drugs. Immunotherapeutics are extremely expensive. It remains to be seen whether the health care systems can provide access to these compounds for all patients. ■

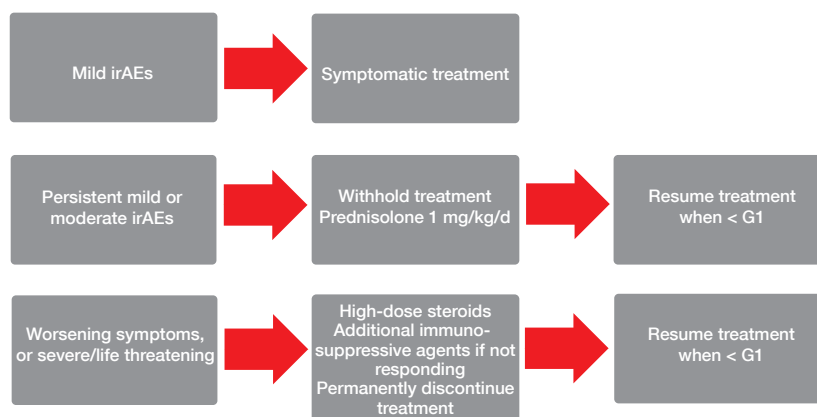
## Immunotherapy: management of toxicity

The basis underlying the toxicities of immune checkpoint inhibitors is their promotion of T-cell activity in a physiological manner. "The amplification of the immune system results in autoimmunity," explained Ross Soo, MD, FRACP, National University Cancer Institute, Singapore.

Common AEs include fatigue, anorexia and arthralgia. Terms that denote immune-related adverse events (irAEs) typically end in -itis or -opathy. CTLA-4 inhibitors, PD-1/PD-L1 inhibitors and their combinations can give rise to fever, chills and lethargy [1]. Skin eruptions are usually of a maculopapular type, and gastrointestinal events include diarrhoea and colitis, with ulceration. Elevations in liver function tests can occur. Potential endocrine complications include hypophysitis, thyroiditis, and adrenal insufficiency. Rarely, neuropathy, nephritis, pneumonitis, Guillain-Barré syndrome, sarcoids, and myasthenia gravis can be observed. The incidence of specific AEs varies slightly according to the mechanism of action of the immunotherapeutic used.

#### Improved tolerability of PD-1/PD-L1 agents

For patients receiving CTLA-4 inhibitor therapy, irAEs can occur within days or months, or even after discontinuation of



**Figure:** General principles of irAE management

the treatment, which is why the follow-up of these patients should continue for several months after their cessation of treatment. Early AEs associated with CTLA-4 therapy include pruritus and skin rash, while hypophysitis and liver toxicity count among the late toxicities. "The risk of AEs naturally increases when these drugs are administered in combination with other agents," said Dr. Soo. A meta-analysis in more than 1,200 patients across 22 trials rated the incidences of all-grade irAEs and grade  $\geq 3$  irAEs with CTLA-4 inhibitor therapy at 72 % and 25 %, respectively [2].

Compared to anti-CTLA-4 treatments, PD-1/PD-L1 inhibitor therapy is generally less likely to cause irAEs. Also,

anti-PD-1 antibodies often show considerably higher tolerability than their chemotherapeutic comparators in clinical studies. In the CheckMate 017 trial, any treatment-related AEs occurred in 86 % with docetaxel, but only in 58 % with nivolumab. For grade 3/4 events, the respective percentages were 55 % and 7 % [3]. Similar numbers were obtained in the CheckMate 057 study that investigated the same agents in patients with a different histology [4]. Notably, (febrile) neutropenia hardly emerges with PD-1 inhibitor therapy, and there are also substantial advantages in terms of non-haematological toxicity (e.g., fatigue, nausea, peripheral neuropathy). AEs of nivolumab tend to cluster within



the first three months of treatment [5]. After that, the incidence decreases markedly. Resolution of AEs is seen in significant percentages.

### What to do when irAEs appear?

The first step that should be taken in the management of irAEs is the identification of alternative causes. Close monitoring is necessary. If no clear-cut alternative cause can be found, all events of an inflammatory nature should be con-

sidered as immune-related. "Just by googling product inserts, physicians can obtain simple information on how to manage toxicities," Dr. Soo said. Moreover, several review articles that outline the management of a range of toxicities and suggest treatment algorithms are available [6–9].

Low-grade AEs are controlled with symptomatic/topical measures (**Figure**). If low-grade events persist or severe AEs occur, systemic corticosteroids should be considered. Potent immunosuppressive drugs are an option in cases

of lack of response to systemic steroids. "Patient education has an important role," Dr. Soo pointed out. Information leaflets on various agents are provided by the pharmaceutical industry.

Overall, increasing expertise in handling immune checkpoint inhibitors has contributed to improved management. "Treatment discontinuation rates due to treatment-related AEs in clinical studies were low," Dr. Soo emphasised. ■

**Source:** Educational session "New challenges in immunotherapy for lung cancer", 18<sup>th</sup> December 2015

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## Intracranial activity of ceritinib in crizotinib-pretreated and crizotinib-naïve ALK-positive NSCLC patients

In 3 % to 5 % of cases, lung cancer is associated with *ALK* rearrangement and can therefore be targeted with the ALK inhibitors crizotinib and ceritinib. While crizotinib is the standard first-line therapy, ceritinib has gained approval for use with patients who are crizotinib-refractory. Ceritinib showed clinical activity in both crizotinib-pretreated and ALK-inhibitor-naïve patients in the single-arm, multicentre, phase II, ASCEND-2 and ASCEND-3 studies [1, 2].

Park et al. presented a combined dataset at the ESMO Asia Congress from both of these studies for the patients with brain metastases at baseline [3]. CNS metastases are a common complication in patients with *ALK*-positive NSCLC. Seventy-one percent and 40.3 % of the patients had brain lesions at the time of

inclusion in ASCEND-2 and ASCEND-3, respectively. Prior radiotherapy to the brain had taken place in 72 % and 54 %, respectively.

At the established dose of 750 mg daily, the median PFS amounted to 6.8 months (ASCEND-2) and 11.0 months (ASCEND-3), by blinded independent central review. The ORRs (as the whole-body response) across these trials were 32.0 % and 60.0 %, respectively. In the patients with active brain lesions selected as the target lesions (e.g., those that progressed following local therapy), the overall intracranial response rates were 39.4 % and 58.8 %, respectively. The intracranial disease control rates exceeded 80 % in both trials.

The safety profile for patients with brain metastases did not differ from that

in the overall patient population. This subgroup analysis shows that ceritinib is feasible in patients with brain metastases, as durable intracranial responses can be expected. ■

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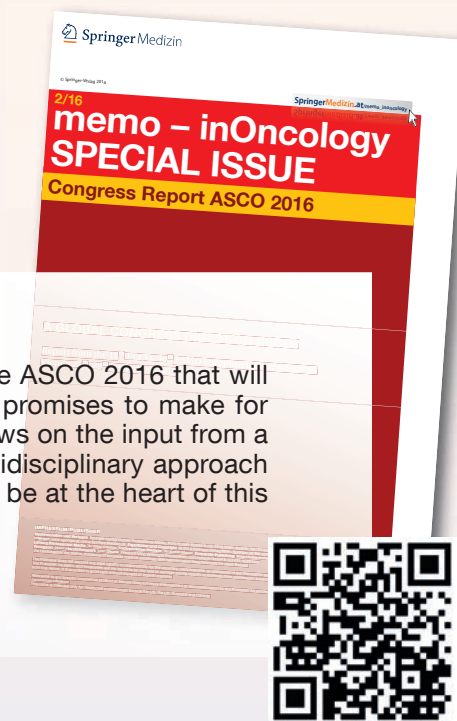
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## Forthcoming Special Issue

This special issue will be offering a synopsis from the ASCO 2016 that will be held in Chicago, in June of this year. The report promises to make for stimulating reading, as the ASCO 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.



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