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Congress Report WCLC 2016

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the International Association for the Study of Lung Cancer (IASLC) 17th World Conference on Lung Cancer, December 4th–7th, 2016, Vienna

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Preface

Dear Colleagues,

From 4th to 7th December, 2016, the IASLC 17th World Conference on Lung Cancer (WCLC) took place in Vienna, Austria, attracting more than 6,500 participants from 93 countries. Scientific insights presented at the IASLC WCLC 2016 are summarised in this memo inOncology congress report that covers a range of topics relating to the diagnosis and treatment of lung cancer.

The mission of the International Association for the Study of Lung Cancer (IASLC) is to conquer thoracic cancers around the world. We attempt to achieve this goal through promoting research and education, and through collaboration with other foundations, patient organisations and health authorities. Major efforts are also made in disseminating and educating the community worldwide and promoting the careers of the next generation of researchers and care-providers. To fund its research and education missions, the IASLC has established a Foundation, and we are funding more grants and fellowships than ever. Projects such as the IASLC Lung Cancer Staging Project, and now the Molecular Staging Project have the potential to change everyday practice. Unlike other organisations that focus on medical oncology or thoracic surgery, we are by design multidisciplinary and address all spheres of the war against thoracic cancers, including tobacco control, prevention, early detection and all aspects of patient support, care and treatment.

The international nature of the IASLC and the pace of progress in the field of lung cancer have prompted us to move annual world conferences, as well as annual regional meetings. We are hoping to make the IASLC WCLC the established platform for the interdisciplinary, international dissemination of the state of the art in lung cancer research. At present, we are focussing on enhancing our activities in Latin America, Africa and the Middle East, and increasing the involvement of Nurses and Allied Health Providers. Multi-lingual educational programmes are being developed.

What really matters, however, is the impact the cancer community has on the patients' lives. The progress in this area has been tremendous. Nowadays, effective and minimally toxic therapy can be offered to an increasing number of patients. Sometimes we can literally rescue patients from the jaws of death and bring them back to a normal quality of life, and I believe that we should be proud of this.

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However, there is still a long way to go, and we need to work hard to convert the responses observed in clinical practice to cures. In this context, the global involvement of a multitude of experts in the field of lung cancer is of particular significance. Everyone is welcome to become a member and work with us in furthering this mission.

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Notable advances in the field of anti-EGFR therapy

The irreversible ErbB family blocker afatinib and the reversible EGFR TKIs gefitinib and erlotinib have been approved as first-line therapies for treatment of NSCLC patients with *EGFR*-sensitising mutations. However, resistance frequently develops, which indicates the need for new agents. The EGFR T790M mutation has been identified as the most common resistance mutation.

The oral, irreversible, third-generation EGFR TKI osimertinib is active in both sensitising and EGFR T790M resistance mutations. This treatment was evaluated in AURA3, the first randomised phase III trial to compare a T790M-selective EGFR TKI with platinum-based doublet chemotherapy in patients with T790M-positive advanced NSCLC progressing on first-line EGFR TKI therapy [1]. Osimertinib was administered at 80 mg once daily (OD) in the experimental arm (n = 279), while patients in the control arm received pemetrexed plus carboplatin or cisplatin, followed by optional pemetrexed maintenance (n = 140). Stable asymptomatic central nervous system (CNS) metastases were allowed.

AURA3: 70 % risk reduction with osimertinib

Osimertinib demonstrated statistically superior and clinically meaningful activity compared to the platinum-pemetrexed therapy. The primary endpoint of investigator-assessed PFS was highly significantly in favour of osimertinib (10.1 vs. 4.4 months; HR, 0.30; $p < 0.001$; **Figure 1**). Progression-free survival (PFS) benefits occurred across all of the subgroups. Patients with CNS metastases at baseline experienced similar reductions in the risk of progression or

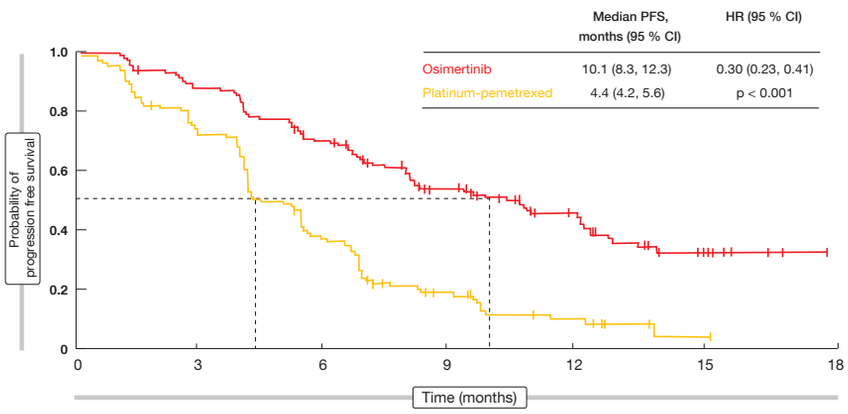

Figure 1: PFS according to investigator assessment in AURA3: pronounced advantage for osimertinib over chemotherapy

death (PFS, 8.5 vs. 4.2 months; HR, 0.32) as those without cerebral lesions (10.8 vs. 5.6 months; HR, 0.40). The objective response rate (ORR) was significantly higher with osimertinib (71 % vs. 31 %; p < 0.001), and the median duration of response was longer (9.7 vs. 4.1 months). Moreover, the tolerability of osimertinib surpassed that of chemotherapy, as possibly treatment-related grade ≥3 adverse events (AEs) occurred less frequently (6 % vs. 34 %). The investigators thus noted that osimertinib represents the new standard of care for patients with EGFR T790M-positive NSCLC following disease progression with first-line EGFR TKI therapy.

According to another analysis of AURA3, the clinical benefits obtained with osimertinib in this trial were independent of whether T790M positivity had been established by testing of tissue or for circulating tumour DNA (ctDNA) [2]. Sensitivity and specificity rates for T790M detection in the plasma using the cobas® EGFR Mutation Test v2 as a reference were 51 % and 77 %, respectively. The analysis revealed high sensitivity and specificity for both exon 19 deletion and L858R mutation. PFS and ORR were similar for T790M-positive patients according to tumour tissue and ctDNA testing. This is a favourable finding, as re-biopsy at disease progression is not always feasible, and can be associated with risks and treatment delays.

LUX-Lung 7: continued benefit with afatinib over gefitinib

The phase IIB LUX-Lung 7 trial was the first prospective, global, randomised study to compare two EGFR-directed therapies (afatinib and gefitinib) head-to-head in the first-line setting. A total of 319 patients with *EGFR*-positive stage IIIB/IV adenocarcinoma of the lung were randomised to either afatinib 40 mg OD or gefitinib 250 mg OD. In the primary analysis, afatinib significantly improved the co-primary endpoints of PFS and time to treatment failure (TTF) compared to gefitinib [3]. The key secondary endpoint, ORR, was also significantly improved. At the WCLC, Park et al. presented the primary overall survival (OS) analysis as well as other updated outcomes [4].

The OS did not differ significantly between these two arms, although a 14 % reduction in the risk of death occurred for afatinib (median OS, 27.9 vs. 24.5 months, for afatinib vs. gefitinib; HR, 0.86; p = 0.2580). The trend favouring afatinib was consistent across pre-specified subgroups, including populations with deletion 19 (30.7 vs. 26.4 months; HR, 0.83) and L858R mutation (25.0 vs. 21.2 months; HR, 0.91). Independently reviewed PFS still showed benefit with afatinib treatment (11.0 vs. 10.9; HR, 0.74; p = 0.0178), as did the updates for TTF (13.7 vs. 11.5 months; HR, 0.75; p = 0.0136) and ORR (73 % vs. 56 %; OR, 2.12; p = 0.002). Median duration of response was 10.1 vs. 8.3 months.

The updated quality-of-life data were also similar between these arms. AEs were predictable and manageable, with equally low rates of treatment discontinuation. Dose reductions of afatinib improved toxicity without compromising efficacy. Patients who received dose reductions within the first 6 months of treatment experienced similar median PFS results as those who were treated with afatinib ≥ 40 mg OD for the first 6 months (12.8 and 11.0 months, respectively).

Findings in elderly patients

As more than one third of patients with lung cancer are at least 75 years old, the efficacy and safety of new agents matters in this population. Treatment can be challenging due to poorer functional status and high comorbidity burden. According to *post-hoc* subgroup analyses of patients aged ≥ 75 and < 75 years in LUX-Lung 7, advanced age did not adversely affect the outcomes achieved with afatinib *versus* gefitinib [5]. PFS and OS findings were consistent across age subgroups **(Figure 2)**.

Afatinib demonstrated a predictable and manageable safety profile. In patients aged ≥ 75 years, no new or unexpected AEs emerged. These results suggest that afatinib can provide effective and tolerable treatment for older patients with *EGFR*-mutant NSCLC.

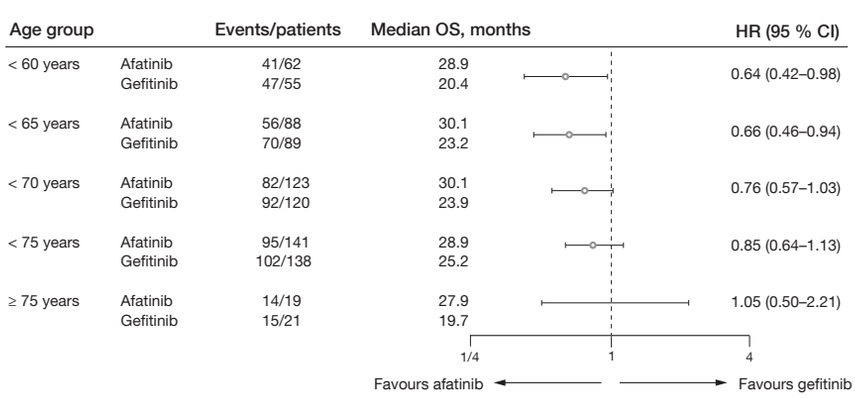

Figure 2: Median OS obtained with afatinib vs. gefitinib in various age groups in the LUX-Lung 7 trial

Predictors of long-term response in LUX-Lung 8

The randomised, open-label phase III LUX-Lung 8 study compared afatinib 40 mg OD and erlotinib 150 mg OD in patients with squamous-cell carcinoma (SCC) of the lung who had progressed after ≥ 4 cycles of platinum-doublet chemotherapy. Here, afatinib significantly improved PFS and OS (HR, 0.81 for both) [6], which prompted its approval for this indication. A group of 15 long-term responders (LTRs) who derived prolonged benefit from afatinib treatment was identified in the LUX-Lung 8 trial. In this cohort, the median treatment duration was 16.6 months. Goss et al. investigated molecular and clinical biomarkers that might be indicative of long-term response to afatinib [7].

The baseline characteristics of the LTRs did not deviate to any meaningful extent from those of the overall afatinib-treated population. Also, the best responses to first-line chemotherapy were similar across these two groups. Median OS and PFS in the LTRs were 23.1 months and 16.2 months, respectively. One patient experienced CR, four patients had PR, and eight patients had SD. Next-generation sequencing was performed for nine of the LTRs and for 132 of the 398 afatinib-treated patients in the overall study population. This analysis showed that certain short variants were more common in the LTRs, such as aberrations in the *ErbB* family, *MLL*, *KEAP1* and *PIK3CA* genes. Copy number aberrations occurred with similar incidence across these two groups. According to the VeriStrat® proteomic assay, a greater proportion of the LTRs was classified as "Good" compared to the overall afatinib-treated population (86 % vs. 62 %). These patients were nearly four times as likely to survive for ≥ 12 months compared to the "VeriStrat®-Poor" patients.

The frequency of common treatment-related AEs in the LTRs was similar to that observed in the overall afatinib-treated population. Afatinib 40 mg OD was maintained in seven of the 15 LTRs, with escalation to afatinib 50 mg in four. Dose reductions did not appear to affect OS adversely. Further studies are required to predict long-term responses to afatinib in patients with SCC of the lung.

In the overall patient population of LUX-Lung 8, however, Felip et al. identified no tumour biomarkers that affected outcome [8]. Although the samples of these patients included multiple genetic aberrations, no biomarkers were predictive of clinical outcomes with afatinib or erlotinib. PFS and OS did not differ significantly between afatinib and erlotinib in the "VeriStrat®-Poor" group. The investigators thus concluded that afatinib is more effective than erlotinib and should be considered as a second-line option in patients with SCC of the lung, regardless of tumour characteristics.

CSF penetration of afatinib

The CNS is a common site for tumour recurrence, probably due to the low penetration of some therapeutic agents through the blood-brain barrier. Patients with brain metastases arising from NSCLC have poor prognosis. Results from the LUX-Lung 3 and 6 studies suggest that afatinib is effective for the treatment of *EGFR*-positive NSCLC patients with brain metastases [9].

Tamiya et al. therefore prospectively analysed the cerebrospinal fluid (CSF) penetration rate of afatinib in 11 patients with *EGFR*-positive NSCLC and leptomeningeal carcinomatosis [10]. They showed that the median CSF penetration rate of afatinib of 1.7 % was higher than previously reported (0.7 %) [11]. The efficacy of afatinib in leptomeningeal carcinomatosis was demonstrated in particular for patients with uncommon *EGFR* mutations, such as exon 18 mutation. With regard to the toxicity, stomatitis, diarrhoea and skin complications required special attention.

Afatinib in medically unfit patients

As the LUX-Lung 3 and 6 trials solely included patients suitable for platinum-based doublet chemotherapy, the efficacy and toxicity of afatinib in patients not eligible for this kind of treatment remained unknown. One study suggested that TKIs can benefit medically unfit *EGFR*-mutant East Asian patients [12]. The single-arm, phase II TIMELY trial was the first on this issue to be conducted in a western population [13]. Thirty-nine patients with NSCLC who were deemed unsuitable for radical treatment or chemotherapy, or who declined the latter, participated in the study. They had either confirmed activating *EGFR* mutation or showed clinical characteristics that were indicative of *EGFR* mutations when no tissue was suitable for genotyping, or genotyping had failed/ was not available. Treatment consisted of afatinib 40 mg OD until progression.

At 6 months, 58 % of all patients were alive and progression-free (primary endpoint). Median PFS and OS were 7.9 and 15.5 months, respectively. In patients with confirmed *EGFR* mutation, PFS and OS were 10.2 months and had not been reached, respectively. Those with suspected *EGFR* mutants fared a bit worse in comparison (4.4 and 10.9 months, respectively), although these PFS and OS results appeared improved

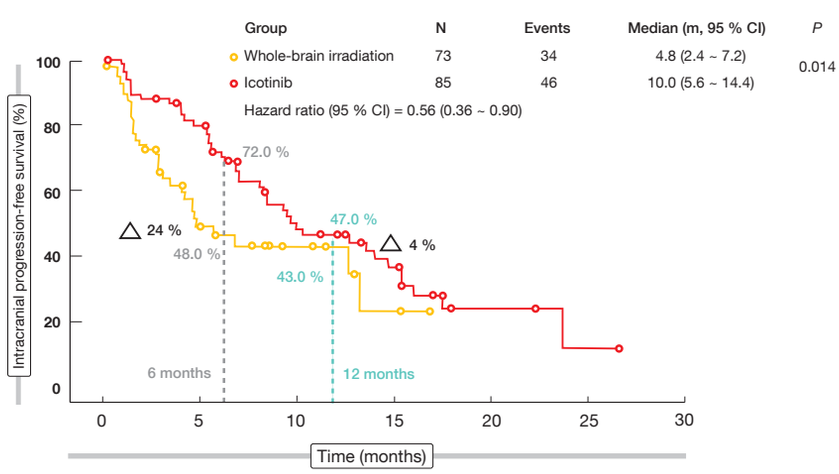

Figure 3: Intracranial PFS with icotinib vs. whole-brain irradiation ± chemotherapy

compared to similar patients who were considered unfit for chemotherapy in the TOPICAL trial [14]. The toxicity rate observed in TIMELY was higher than that usually seen in fitter patients. Twenty-three of the 39 patients experienced at least one grade ≥ 3 toxicity.

Icotinib is superior to brain irradiation

Whole-brain irradiation (WBI) has been a standard of care for NSCLC patients with brain metastases. The randomised phase III BRAIN trial evaluated the EGFR TKI icotinib at 125 mg three times daily compared to WBI with or without chemotherapy in EGFR-TKI–naïve patients with *EGFR*-mutant, advanced NSCLC and brain metastases at ≥ 3 sites [15]. In both arms, more than 80 % of the patients did not experience any symptoms related to their cranial lesions. Eighty-five and 73 patients received icotinib and WBI, respectively. Intracranial PFS was defined as the primary endpoint. BRAIN represents the first phase III trial to compare an EGFR TKI with WBI.

According to this analysis, icotinib significantly improved intracranial PFS over WBI (median, 10.0 vs. 4.8 months; HR, 0.56; p = 0.014). At 6 months, there was a 24 % difference in favour of icotinib (72.0 % vs. 48.0 %; **Figure 3**). A significant benefit was also observed for PFS (6.8 vs. 3.4 months; HR, 0.44; p < 0.001). Six-month PFS rates achieved with icotinib and WBI were 55.0 % and 22.0 %, while at 1 year, 19.0 % *versus* 9.0 % of patients were alive and progression free. The OS analysis did not reveal any difference between the two arms.

The icotinib treatment gave rise to significant benefits regarding intracranial ORR (67.1 % vs. 40.9 %; p < 0.001) and intracranial DCR (84.7 % vs. 67.1 %; p = 0.014). This was also true for overall ORR (55.0 % vs. 11.1 %; p < 0.001) and overall DCR (78.8 % vs. 54.8 %; p = 0.001). With respect to treatment-related toxicity, patients in the icotinib arm did better than the control group, with significant differences in favour of the EGFR TKI noted for AEs of all grades. Based on these data, the authors concluded that icotinib should be used in first-line treatment of advanced *EGFR*-mutant NSCLC patients with brain metastases.

Clinical significance of p53 mutation

Griesinger et al. reported the first data obtained in a homogeneously TKI-treated patient population with *EGFR*-activating mutations, to show that when classified as pathogenic *versus* non-pathogenic/ wild-type, p53 mutation is a negative predictive marker for PFS and OS [16]. Usually, p53 mutations are classified as either disruptive or non-disruptive. Here, the DNA-contact mutations R273C, R273G and R248Q were reclassified as pathogenic, as were missense mutations located inside loops L1-L3 of p53, along with sequence substitutions that reached a score of C65 according to the missense analysis programme Align-GVGD. All other p53 mutations located outside loops L1-L3 were scored as non-pathogenic.

According to the OS and PFS analyses, the impact of the p53 mutations was significant. In those with non-pathogenic/ wild-type mutations, median OS was 42 months, while those with pathogenic mutations had an OS of 23 months. For PFS, this was 18 and 11 months, respectively. As is known, patients with exon 19 mutation have a better prognosis than those with exon 21 mutation, but the prognostic and predictive impact of the p53 mutation held true for both of these groups. Also, p53 mutations were demonstrated to be a negative predictive factor irrespective of patient clinical characteristics (e.g., ECOG performance status, CNS metastases, smoking status). The investigators noted that patients with p53-mutated tumours who receive EGFR TKIs might require different therapy management. There is a need for further therapeutic approaches in this patient group, such as combinations of EGFR TKIs with other drugs.

Another analysis found that apart from the major resistance mutation T790M, the minor mutations L792F and C797S can develop in afatinib-resistant cells [17]. L792F and C797S appear to be sensitive to dacomitinib and erlotinib, respectively. To enable treatment with these agents, the authors recommended testing for these minor mutations in clinical practice when resistance to afatinib occurs. ■

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Emerging treatments in *ALK*-positive NSCLC: new options, but also new challenges

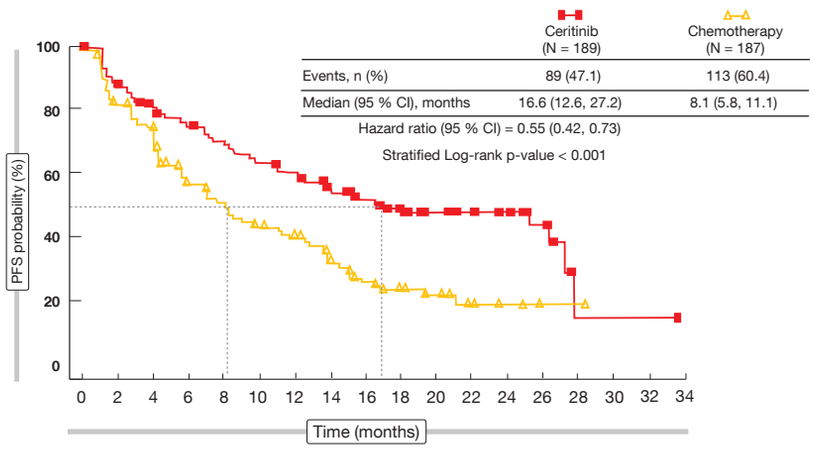

Figure: Primary endpoint in ASCEND-4: PFS advantage with ceritinib over chemotherapy

Treatment with the ALK tyrosine kinase inhibitor (TKI) crizotinib has been established as a standard first-line option in patients with *ALK*-rearranged advanced NSCLC. Before the advent of crizotinib, a platinum–pemetrexed doublet followed by pemetrexed maintenance was standard of care in non-squamous NSCLC. However, after an initial response to crizotinib, acquired resistance invariably develops due to multiple mechanisms, which can include secondary mutations in the *ALK* tyrosine kinase domain.

A range of newer-generation ALK inhibitors are now available or are currently under development. These include ceritinib, alectinib, brigatinib, ensartinib, entrectinib and lorlatinib. All of these have increased ALK-inhibition potencies and activities against the mutations that confer resistance to crizotinib. Also, many of these show improved CNS penetration over crizotinib.

First-line ceritinib: ASCEND-4

Ceritinib demonstrated robust anti-tumour activity in crizotinib-naïve and crizotinib-refractory patients with *ALK*-positive advanced NSCLC in the single-arm phase I and II ASCEND trials (ASCEND-1–3) and in a randomised phase III study (ASCEND-5). The randomised, global, open-label, ASCEND-4 phase III study that was presented in the Presidential Symposium at the WCLC compared first-line ceritinib 750 mg/day with platinum and pemetrexed chemotherapy, followed by pemetrexed maintenance, in untreated patients [1]. PFS by blinded independent radiological review was the primary endpoint. A total of 376 patients were enrolled in the study, with 189 randomised to ceritinib and 187 to chemotherapy. Approximately one third in each arm had brain metastases. Prior brain radiotherapy had been administered in 40 % of these patients.

The study was positive with respect to its primary endpoint: PFS with ceritinib was significantly longer than with chemotherapy (16.6 vs. 8.1 months, respectively; HR, 0.55; $p < 0.001$; **Figure**). Most of the pre-defined subgroups derived greater PFS benefit from ceritinib than from chemotherapy. The differences in OS were not significant, but they trended in favour of ceritinib. At 24 months, OS rates were 70.6 % *versus* 58.2 %. The ceritinib ORR surpassed that obtained with chemotherapy by over 45 % (72.5 % vs. 26.7 %). Also, the patients responded more rapidly with ceritinib, as the median times to first response were 6.1 and 13.4 months, respectively. Median duration of response was 23.9 months *versus* 11.1 months, respectively. Patients with and without brain metastases benefited from ceritinib, with PFS improved in both groups (HRs, 0.70 and 0.48, respectively). The ALK inhibitor treatment gave rise to a superior intracranial response rate compared to chemotherapy (72.7 % vs. 27.3 %), and the ceritinib intracranial benefit was durable, with a median duration of response of 16.6 months.

According to patient-reported outcomes, the lung cancer symptom scores were significantly improved *versus* chemotherapy, and the time to definitive deterioration of lung-cancer-specific symptoms was prolonged. The safety profile of ceritinib was consistent with previous studies, with diarrhoea, nausea and liver enzyme elevations as the most common AEs. Management included dose adjustments or dose interruptions/ delays, as well as concomitant medication.

J-ALEX: superiority of alectinib over crizotinib

In addition to ceritinib, alectinib is a standard option in the setting of progression on crizotinib treatment. The Japanese J-ALEX trial enrolled 207 patients who had received at most one prior line of chemotherapy. They were randomised to either first-line alectinib 300 mg BID (i.e., standard alectinib dose in Japan) or crizotinib 250 mg BID [2]. Patients with treated or asymptomatic brain metastases were also included.

The study was strongly positive. Alectinib proved superior to crizotinib with respect to the primary endpoint, which was independently reviewed PFS (not reached for alectinib vs. 10.2 months for crizotinib; HR, 0.34; $p < 0.0001$). Multiple stratified Cox regression analysis demonstrated consistent treatment effects that favoured alectinib over crizotinib, and this also extended to patients with brain metastases. As the CNS is a common site of disease progression in patients with *ALK*-positive NSCLC, the activity of new ALK-inhibiting compounds is of particular importance in

TABLE
Responses according to prior radiation in patients with measurable and non-measurable CNS disease receiving alectinib 600 mg BID

Response	Prior radiation (n = 95)	No prior radiation (n = 41)
CNS objective response rate, %	37.9	58.5
Complete response, n (%)	19 (20.0)	20 (48.8)
Partial response, n (%)	17 (17.9)	4 (9.8)
Stable disease, n (%)	47 (49.5)	10 (24.4)
Progressive disease, n (%)	9 (9.5)	3 (7.3)
CNS disease control rate, %	87.4	82.9

this respect. There was an imbalance between the two treatment arms regarding the number of patients without and with CNS disease, as this was not a stratification factor in J-ALEX. More patients with untreated brain metastases enrolled on the alectinib arm.

According to separate PFS analyses for patients without and with CNS disease at baseline, both groups experienced highly significant benefits with alectinib compared to crizotinib. The risk reductions amounted to 63 % in those without brain lesions (median PFS, 20.3 vs. 10.0 months; HR, 0.37; p = 0.0001) and 91 % in those with pre-existing CNS metastases (not reached vs. 10.2 months; HR, 0.09; p = 0.0062). Alectinib-treated patients in the brain lesion group also fared significantly better with regard to time to progression of CNS disease (HR, 0.16; p = 0.0492). Similarly, for those without brain metastases at baseline, time to appearance of CNS disease was significantly longer with alectinib (HR, 0.17; p = 0.0019). Overall, alectinib showed greater activity for existing CNS disease, and greater potential to prevent the development of new CNS lesions.

Updated analysis on CNS results obtained with alectinib

These data are supported by a pooled analysis of two phase II trials. The pivotal NP28761 and NP28673 studies investigated alectinib 600 mg BID after progression on crizotinib treatment. NP28761 was conducted in North America and NP28673 globally. The results demonstrated high response rates and durable responses [3, 4]. A pooled analysis of these two trials performed with the data cut-off on 27 April, 2015, yielded a CNS ORR of 64.0 % and a duration of CNS response of 10.8 months in patients with measurable CNS disease at baseline [5].

At the WCLC, Ou et al. presented updated pooled data using 2016 data cut-offs to further evaluate the CNS efficacy of alectinib in these two trials [6]. According to this analysis, CNS ORR was 64.0 % in patients with measurable CNS disease and 44.1 % in those with measurable and non-measurable disease combined. Complete responses were achieved in 22.0 % and 28.7 %, respectively, with CNS disease control in 90.0 % and 86.0 %, respectively. These CNS responses were also durable, as they lasted for 11.1 and 13.8 months, respectively.

Moreover, the pooled data show that alectinib is active in the CNS regardless of prior radiation. Seventy percent of patients with measureable and non-measurable CNS disease had received prior radiotherapy; here, CNS ORR and CNS DCR were 37.9 % and 87.4 %, respectively. For those without prior radiotherapy, these were 58.5 % and 82.9 %, respectively, and complete responses occurred in 48.8 % (**Table**).

Brigatinib & lorlatinib

Likewise, the investigational next-generation ALK inhibitors brigatinib and lorlatinib have been shown to have pronounced activities, particularly in the CNS. An update from the pivotal randomised ALTA phase II trial that evaluated brigatinib at two doses (90 mg and 180 mg OD) in crizotinib-refractory patients demonstrated substantial efficacy and an acceptable safety profile in both arms [7]. At brigatinib 180 mg, ORR was 54 % according to the Independent Review Committee, and OS probability at 1 year was 82 %. Median PFS obtained with 180 mg surpassed PFS in the 90 mg arm considerably (15.6 vs. 9.2 months, respectively; HR, 0.58). When treated with brigatinib 180 mg, patients with measurable brain metastases experienced an intracranial ORR of 67 %.

A separate analysis of an ongoing phase I/II trial and the ALTA study assessed brigatinib activity in patients with intracranial CNS metastases, which yielded the high intracranial response rates of 53 % and 67 % (at brigatinib 180 mg) in patients with measurable metastases in the two trials [8]. Also, the median intracranial PFS findings were robust, at 14.6 and 18.4 months.

For lorlatinib, a phase I dose-finding study demonstrated significant clinical activity in patients with both *ALK*-positive and *ROS1*-positive NSCLC, most of whom had brain metastases and had received at least one prior ALK TKI [9]. In the *ALK*-positive group, ORR was 46 %, and median PFS was 9.6 months. Patients with brain metastases and target lesions achieved intracranial responses in 42 %. Durable responses were noted in patients who had received two or more prior ALK TKIs. Lorlatinib was generally well tolerated, with the most frequent treatment-related toxicity of hypercholesterolaemia, which was manageable with statin therapy. The phase II portion of this trial is ongoing at 57 centres worldwide.

Treatment selection – the current perspective

The growing armamentarium in the field of ALK-targeted agents raises several questions with respect to patient selection and selection of ALK TKIs. "The observation that many crizotinib-resistant tumours remain ALK-dependent over time provides the rationale for sequential therapy," noted Benjamin Solomon, MBBD, PhD, Peter MacCallum Cancer Centre, Melbourne, Australia [10]. Retrospective analyses have suggested survival benefits with sequential ALK inhibitor therapies in *ALK*-positive NSCLC patients [11, 12].

In the light of the recent clinical trials, the optimal first-line treatment of advanced *ALK*-positive NSCLC remains to be established, although it appears likely that next-generation inhibitors will be used from the beginning, instead of crizotinib. "The ongoing phase III studies will provide us with much more data to definitively address this ques-

tion soon," Dr. Solomon pointed out. For now, following first-line crizotinib therapy, second-generation ALK inhibitors can be used, such as ceritinib, alectinib and brigatinib. When progression occurs with these agents, the choice of the third-line drug depends on factors such as CNS activity and the prevailing mutations at the time of progression. "One type of ALK inhibitor may be more effective in the CNS than another," Dr. Solomon explained. Activities also vary with regard to mutations. For instance, the I1171T mutation confers resistance to alectinib, but not to ceritinib. The spectra of mutations against the newer ALK inhibitors differ from the mutation spectrum found in crizotinib-resistant specimens [13]. Among the currently available ALK inhibitors, lorlatinib has the widest range of mutation coverage, which includes the G1202R mutation that confers resistance to crizotinib, ceritinib and alectinib. Third-line agents such as lorlatinib can therefore be an option in cases of second-generation ALK TKI resistance mutations and/ or CNS disease.

As Dr. Solomon stated, assessment of *ALK* mutations using strategies such as liquid biopsy may eventually guide the choice of the ALK TKI therapy. Combination strategies may be required to overcome off-target mechanisms of resistance. "This potentially includes combinations with immunotherapy." ■

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Liquid biopsy in the context of *EGFR* and other mutations

Compared to tissue biopsy and re-biopsy, liquid biopsy offers several advantages, including minimal-invasiveness, the opportunity for serial measurements over time to monitor tumour response, and detection of resistance mutations in the plasma prior to radiographic detection [1]. The issue of tumour heterogeneity, which is an important factor in therapeutic failure, is also considered. Driver mutations can be identified with high sensitivity and specificity, thus improving delivery of personalised medicine. Although there remain controversial issues such as standardisation, validation of different technologies, and concordance with tissue molecular profile results, liquid biopsy has emerged as an alternative tool for the management of advanced NSCLC patients.

High concordance rate between plasma and tissue

One of several analyses presented at the WCLC that confirm liquid biopsy as an emerging standard was that of Mack et al., who assessed the Guardant360 panel for population-scale genomics (in comparison with The Cancer Genome Atlas), clinical accuracy, and clinical utility [2]. Guardant360 testing allows for digital sequencing of critical exons in 73 genes based on circulating tumour DNA (ctDNA). The cohort comprised 8,388 patients with stage III/IV adenocarcinoma (n = 4,142) or NSCLC-NOS (n = 4,246), with 9,202 samples taken. A median timespan of 177 days had passed between initial diagnosis and ctDNA collection. Tissue information was available in a subset of patients. It should be noted that this was not a random cross-section of patients, as the analysis was enriched for patients progressing on targeted agents. They were generally being treated in the second or later lines.

The overall detection rate of alterations was 87 %, with a median number of three alterations per sample (range, 0-93). Mutations detected in the plasma showed similar frequency and distribution as those reported in the tissue, which applied to truncal mutations present in all lineages of the tumour. The ctDNA fusion patterns mirrored tumour tissue, according to Guardant360. In patients with adenocarcinoma, *EGFR* mutations were found in 26.4 % of cases **(Table)**. Exon 19 deletions constituted most of the *EGFR* driver mutations (52 %), followed by L858R mutations (34 %) and exon 20 insertions (4 %).

As already known, driver mutations were mutually exclusive to a statistically highly significant degree. For instance, when *EGFR* mutation was present, *KRAS* mutation was not, and *vice versa*. Cases of overlap might be due to the emergence of secondary resistance mutations.

Increase in biomarker yield of 65 %

Clinical accuracy was determined in a subset of 543 marker-positive cases where tissue information was available. Here, positive predictive values ranged between 92 % and 100 % according to the type of mutation. All of the patients with positive plasma samples for *KRAS*, $BRAF^{V600E}$ and *MET* E14 skipping mutations also had these mutations in their tumour tissue. For *ALK*, *RET* and *ROS1* fusions, 92 % did not show positive tissue results; these were most likely false negatives. Forty percent of *ALK* fusion cases and 50 % of *EGFR*-positive cases had one potentially actionable resistance target at progression. Overall, the plasma analysis conferred additional benefit, as ctDNA next-generation sequencing increased the biomarker yield by 65 %. This corresponded to 252 additional actionable biomarkers. Oncogenic drivers were detected in 29 % of cases of under-genotyped or unevaluable tissue.

Santos et al. also used Guardant360 testing for liquid biopsy assessment in 100 consecutive patients with stage IV or recurrent adenocarcinoma [3]. Tissue molecular profile results were obtained or recovered from each subject for purposes of comparison with their liquid biopsy counterparts. The investigators showed that agreement between the two methodologies with regard to the type of aberration was greatest for *EGFR* mutations (68 %). This was the case even though circulating DNA testing had been performed months or even years after tumour tissue testing. None of the liquid biopsies was performed at the time of diagnosis or tumour biopsy.

The rate of identification of abnormalities was higher with liquid biopsy than with tissue testing. Forty-six percent of patients with *EGFR* aberrations according to liquid biopsy had actionable mutations. Sixteen out of 35 patients with *EGFR* alterations showed mutations or variants identified by liquid biopsy only; in 5 of these 16 cases, actionable *EGFR* mutants were identified exclusively by use of liquid biopsy.

T790M mutation detection

In the TIGER-X phase I/II trial, combined *EGFR* mutation testing of urine and plasma was performed and analysed [4]. TIGER-X enrolled 548 patients with activating *EGFR* mutations who had already been treated with EGFR-directed TKIs. They received the EGFR TKI rociletinib, which is no longer in clinical development. In this trial, 540 tissue samples, 482 plasma samples and 213 urine samples were submitted for pre-treatment *EGFR* testing. The analysis contained 174 matched tissue, plasma and urine samples.

TABLE
Genomic landscape according to circulating DNA in patients with adenocarcinoma who were progressing on targeted agents

Alteration	N	%
***EGFR* mutations**	1,361	26.4
***ALK* fusion**	65	1.3
***RET* fusion**	45	0.9
***ROS1* fusion**	9	0.2
***MET* E14 skipping mutations**	19	0.4
***BRAF* mutations**	139	2.7
***ErbB2* mutations**	119	2.3
***KRAS* mutations**	888	17.2
***MET* amplification**	295	5.7
***ErbB2* amplification**	229	4.4

Figure: Increase in T790M detection with combined use of urine and plasma testing (170 T790M-positive cases)

Non-invasive urine and plasma T790M detection was demonstrated to be highly sensitive. For both plasma and urine testing, sensitivity exceeded 80 %. Even higher rates occurred for combined testing, where the sensitivity was 96.6 %. For the 174 matched tissue, plasma and urine specimens, T790M positivity by any one specimen type was 97.7 %. Combined urine and plasma testing identified more T790M-positive cases than tissue testing alone **(Figure)**. Response rates observed with rociletinib were similar, regardless of whether T790M mutations were detected by liquid biopsy or tissue biopsy.

Moreover, the analyses showed that T790M mutations were more readily detected in the plasma of patients with extrathoracic lesions (M1b) than in those who had only intrathoracic (M1a/M0) disease. However, combined urine and plasma testing allowed for sensitive detection regardless of disease state. Sensitivity was 90.7 % and 95.8 % in patients with M1a/M0 and M1b disease, respectively. The authors concluded that the combined analysis of urine and plasma should be considered prior to tissue testing in EGFR-TKI-resistant NSCLC patients, including those with extrathoracic metastases. ■

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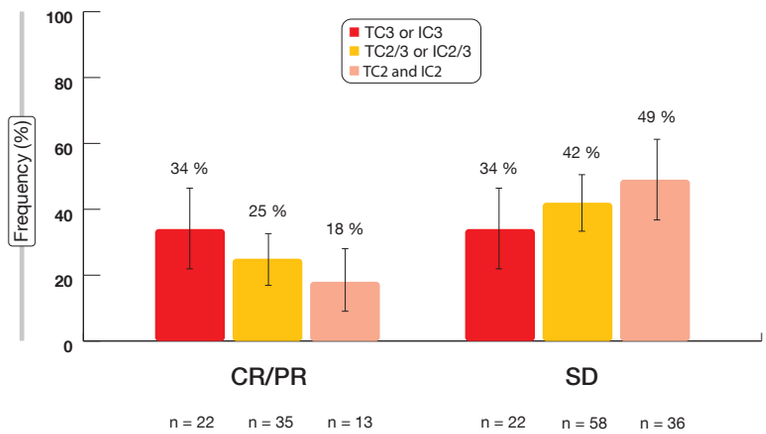
Immunotherapy: novel anti-PD-L1 antibodies & various combination regimens

OAK subgroup analyses

As compared to anti-PD-1 antibodies, the advantage of antibodies directed against PD-L1 is that they can inhibit PD-1/ PD-L1 interactions while leaving the PD-1/ PD-L2 pathway intact, thus potentially preserving peripheral immune homoeostasis. OAK was the first randomised phase III trial to assess an anti-PD-L1 agent in advanced NSCLC. Patients with locally advanced or metastatic NSCLC received either atezolizumab 1,200 mg every 3 weeks or docetaxel. Prior to the trial, they had already been treated with one or two lines of chemotherapy, including at least one platinum-based regimen. The population was enrolled irrespective of PD-L1 status, and stratified according to PD-L1 expression. OAK had two primary endpoints: OS in the ITT population, and OS in patients with PD-L1 expression on ≥ 1 % of tumour cells or infiltrating immune cells. Cross-over was not permitted, which is of relevance for the interpretation of the OS data.

The primary analysis was presented at the ESMO Congress 2016. Here, OAK met both of the primary endpoints [1]. In the ITT population, atezolizumab treatment resulted in a relative reduction in mortality compared to docetaxel of 27 % (median OS, 13.8 vs. 9.6 months; HR, 0.73; p = 0.0003). Also, atezolizumab improved survival at all levels of PD-L1 expression, with the greatest benefit for the patients with the highest PD-L1 expression. However, atezolizumab also improved survival in patients whose tumour did not express PD-L1.

Subgroup analyses conducted in the OAK trial to evaluate the efficacy of atezolizumab in several clinically relevant subgroups revealed broad efficacy of this treatment [2]. OS benefits were observed regardless of PD-L1 expression levels, as measured by immunohistochemistry (IHC) or gene expression, and of histology (non-squamous *vs.* squamous) across PD-L1 expression levels, and for all age groups. OS improvement also occurred in never-smokers and in patients with brain metastases at baseline. On the other hand, docetaxel was more effective than atezolizumab in the subgroup of patients with *EGFR* mutation, while wild-type patients fared better with atezolizumab. This lack of improved efficacy of atezolizumab relative to docetaxel in the *EGFR*-mutant population has already been noted for other in-pathway agents [3].



CR, complete remission; PR, partial remission; SD, stable disease
TC3 or IC3: TC ≥ 50 % or IC ≤ 10 % PD-L1–expressing cells
TC2 and IC2: ≥ 5 % but IC < 10 % and TC < 50 % PD-L1–expressing cells
TC2/3 or IC2/3: TC or IC ≥ 5 % PD-L1–expressing cells, respectively

Figure 1: Response rates with first-line atezolizumab in the BIRCH trial, according to PD-L1 expression status

BIRCH: promising first-line efficacy of atezolizumab

The single-arm phase II BIRCH study evaluated atezolizumab monotherapy in PD-L1–selected patients with locally advanced or metastatic NSCLC. This trial had three arms, to investigate atezolizumab at a dose of 1,200 mg every 3 weeks as first line, second line, and third/ later lines. PD-L1 expression on tumour cells (TC2 or TC3) and tumour-infiltrating immune cells (IC2 or IC3) was examined by IHC. The primary efficacy endpoint, which related the ORRs to historical controls, has already been met. Garassino et al. presented the data of an exploratory analysis that assessed the first-line portion of the trial [4]. This cohort comprised 138 patients. In this group, 47 % showed the highest PD-L1 tumour expression (TC3 or IC3). Fifty-three percent of the patients had TC2 and IC2.

First-line atezolizumab showed promising monotherapy efficacy. The overall population obtained objective responses and stable disease (SD) in 25 % and 42 %, respectively **(Figure 1)**. In the TC3 or IC3 cohort, ORRs and SD rates were each 34 %. For those in the TC2 and IC2 cohort, these were 18 % and 49 %, respectively. Responses lasted for 16.5 months in the overall population, with the median duration of response of 12.3 months in the TC2 and IC2 population; this has not been established for the TC3 or IC3 cohort yet. The ORR benefit of atezolizumab extended to patients with both mutant and wild-type status for *EGFR* and *KRAS*, although the respective patient numbers are small. These results indicate that atezolizumab monotherapy has durable efficacy in the first-line setting.

Median PFS was 7.3 months in the overall population, with similar results across the different levels of PD-L1 expression. After a median follow-up of 22.5 months, median OS was 23.5

TABLE
ATLANTIC: anti-tumour activity of durvalumab in Cohorts 2 and 3

Endpoint	Cohort 2		Cohort 3
	PD-L1 low/ negative (< 25 %) (n = 93)	PD-L1 high (≥ 25 %) (n = 146)	PD-L1 ≥ 90 % (n = 68)
ORR, %	7.5	16.4	30.9
Complete response, %	0	0.7	0
Partial response, %	7.5	15.8	30.9
Stable disease ≥ 8 weeks, %	29.0	34.9	17.6
Progressive disease, %	63.4	47.9	51.5
Not evaluable, %	0	0.7	0
Median duration of response, months	NR	12.3	NR
Disease control rate at ≥ 6 months, %	20.4	28.8	38.2

months. Again, OS trends were comparable across the PD-L1 expression subgroups, although the median OS estimates are not mature yet. The proportion of patients still alive at 1 year in the overall population was 66.4 %. *EGFR* and *KRAS* mutation status did not affect these results. The safety profile was similar to other atezolizumab NSCLC studies, and atezolizumab was well tolerated. Ongoing phase III trials, such as IMpower110, are evaluating atezolizumab compared to chemotherapy in the first-line setting in PD-L1–selected patients.

Durvalumab activity beyond second line in the ATLANTIC trial

Like atezolizumab, durvalumab falls into the category of anti-PD-L1 antibodies. Durvalumab was tested in the open-label, single-arm, phase II ATLANTIC trial at a dose of 10 mg/kg 2-weekly, for up to 12 months [5]. The patients who participated in the trial had at least two prior systemic treatment regimens, including one platinum-based chemotherapy. Initially, the protocol was designed for all comers, but after an amendment, the patient selection was restricted to those with highly PD-L1–expressing tumours. The population consists of three cohorts. Cohort 1 (n = 111) includes patients with *EGFR* mutation/ *ALK* aberration and high PD-L1 expression (≥ 25 % of tumour cells). Patients in Cohorts 2 and 3 have *EGFR*/ *ALK* wild-type. In Cohort 2 (n = 265), PD-L1 expression levels of ≥ 25 % on tumour cells and low/ negative PD-L1 expression (< 25 %) prevails. Cohort 3 (n = 68) includes patients with PD-L1 expression levels ≥ 90 %. The cohorts were independent, and Cohorts 2 and 3 were enrolled sequentially.

In this heavily pre-treated metastatic NSCLC population, durvalumab treatment showed activity and gave rise to durable responses. Stronger PD-L1 expression appeared to be associated with higher response rates. In Cohort 2, the ORRs for patients with low/ negative and high PD-L1 expression were 7.5 % and 16.4 %, respectively **(Table)**. In Cohort 3, the ORR increased to 30.9 %. Disease control rates at ≥ 6 months were 20.4 %, 28.8 % and 38.2 %, respectively. Median duration of response had not been reached yet in Cohort 2 patients with low/ negative expression or in Cohort 3, and was 12.3 months in Cohort 2 patients with high expression. The ORR benefit became apparent across the subgroups; of note, it was independent of the line of treatment and the presence of CNS metastasis.

The groups with low/ negative and high PD-L1 expression in Cohort 2 experienced median OS of 9.3 and 10.9 months, respectively. These results corresponded to 1-year OS rates of 34.5 % and 47.7 %, respectively. For Cohort 3, OS had not been reached yet, and 50.8 % of patients were alive at 1 year. Most AEs were classified as low grade, and immune-mediated AEs proved manageable. The authors concluded that these results are consistent with those obtained with other anti-PD-1/ PD-L1 therapies in metastatic NSCLC. Ongoing phase III trials will clarify the role of durvalumab alone or in combination with the CTLA-4 antibody tremelimumab.

Quadruple approach: chemotherapy plus combined immunotherapy

Durvalumab in combination with the CTLA-4 antibody tremelimumab was investigated in the IND.226 dose-escalation trial that focussed on quadruple therapy, thus combining chemotherapy with two immuno-oncological agents. This study is attempting to amplify the benefits of chemotherapy plus immunotherapy by adding not only a PD-L1 inhibitor, but also a CTLA-4 inhibitor. IND.226 includes patients with solid tumours and uses multiple chemotherapy backbones. Twenty-seven patients of the total cohort have been diagnosed with non-squamous NSCLC. They are PD-L1–unselected. Durvalumab 15 mg/kg 3-weekly and tremelilumab 1 mg/kg (multiple doses, 6-weekly) or 3 mg/kg (3 doses, 6-weekly) are being administered together with pemetrexed and cisplatin.

For safety, which is the primary endpoint of this trial, no significant additional toxicity was observed beyond what can be expected from chemotherapy and checkpoint inhibitor therapy with a CTLA-4 and a PD-L1 antibody [6]. As this is a phase I safety study, not all patients were required to have measurable disease. To date, 16 of 26 patients (61.5 %) have experienced partial responses. Stable disease has occurred in seven cases. Treatment is ongoing in many of these patients.

Overall, it was shown that durvalumab and tremelimumab can be safely combined with full doses of pemetrexed/ cisplatin chemotherapy. Future PD-L1 subset analyses will be performed. A phase II randomised follow-up study will compare platinum-based doublet chemotherapy plus durvalumab/ tremelimumab with durvalumab/ tremelimumab alone, in the first-line setting.

JAVELIN: avelumab in a range of solid tumours

Avelumab is another anti-PD-L1 antibody, and it is being tested in the international, phase I, multi-cohort, dose-escalation and dose-expansion JAVELIN Solid Tumor trial. This study enrolled patients with a range of malignancies, which include thoracic cancers and tu-

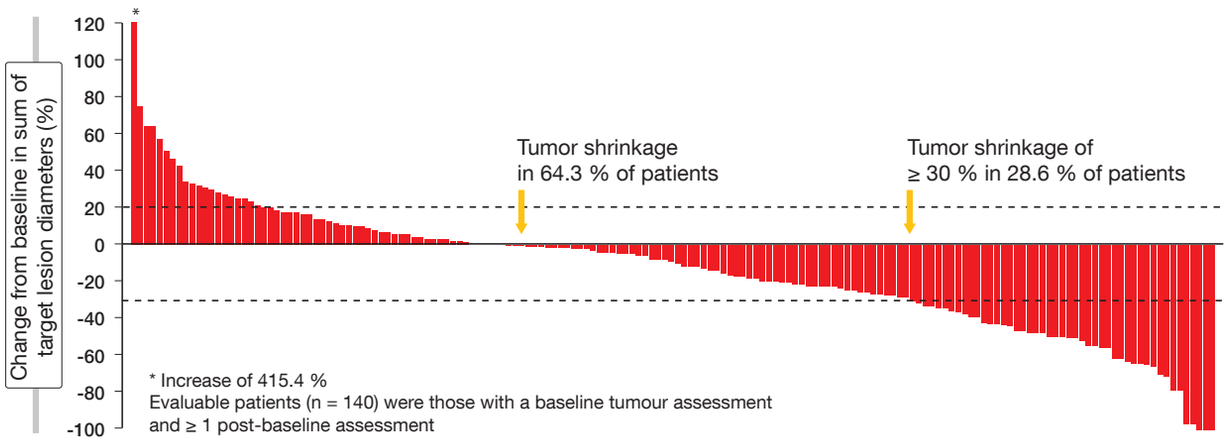


Figure 2: Waterfall plot from the JAVELIN study depicting the tumour shrinkage obtained with avelumab

mours of the skin, head and neck, genitourinary tract, and gastrointestinal tract. Across all of the cohorts, more than 1,700 patients are receiving avelumab 10 mg/kg 2-weekly in the dose expansion phase. Two cohorts with stage IV or recurrent NSCLC have been included; here, patients are treated with avelumab either in the first-line (n = 156) or second-line (n = 184) setting.

At the WCLC, the findings on safety and clinical activity of avelumab in the first-line cohort were reported [7]. These patients are unselected for PD-L1 expression and do not have activating *EGFR* mutations or *ALK* translocations. PD-L1 expression is positive in 56.4 % and negative in 14.7 %. Avelumab was shown to be well tolerated. Ten percent of the patients experienced potentially immune-related AEs, but only one patient developed a grade 3 event. No grade 3/4 pneumonitis occurred; grade 1/2 pneumonitis was observed in only four patients (2.6 %).

This early analysis has revealed durable anti-tumour activity of avelumab monotherapy. Complete and partial responses occurred in 22.5 %. Forty-three percent of patients experienced stable disease, which added up to a disease control rate of 65.4 %. The majority of patients showed tumour shrinkage **(Figure 2)**. At data cut-off, 68.6 % of responses were ongoing. For PFS, the analysis yielded a median of 17.6 weeks, with a 24-week PFS rate of 37.2 %.

Additional follow-up will further characterise the clinical benefits of avelumab therapy. The analysis of PD-L1 expression as a predictive biomarker for avelumab is ongoing. Currently, a phase III trial is comparing avelumab monotherapy with a platinum-based doublet chemotherapy in untreated, PD-L1–selected NSCLC patients.

Long-term outcomes from CheckMate 012

The CheckMate 012 trial evaluated the anti-PD-1 antibody nivolumab alone *versus* two schedules for the combination of nivolumab and the CTLA-4 immune checkpoint inhibitor ipilimumab. This treatment was administered as a first-line strategy in patients with stage IIIB/IV NSCLC of any histology. The nivolumab-only arm (n = 52) received nivolumab 3 mg/kg every 2 weeks. In the two combination arms, nivolumab and ipilimumab were administered at doses of 3 mg/kg 2-weekly and 1 mg/kg, respectively, with one arm receiving ipilimumab every 12 weeks (n = 38), and the other, every 6 weeks (n = 39). PD-L1 expression status was assessed. Approximately 70 % of the patients in each arm had PD-L1 expression ≥ 1 %. The primary endpoint of CheckMate 012 was safety and tolerability. Gettinger et al. presented the long-term outcomes of CheckMate 012 at the WCLC [8].

After an additional follow-up of 6 months in the combination cohorts, the rates of treatment-related AEs and the safety profile remained similar to results reported previously. Treatment-related deaths did not occur. Both nivolumab monotherapy and the combinations demonstrated activity, with the combined administration resulting in higher ORRs, longer PFS, and numerically higher 1-year OS rates. At 2 years, ORR was 23 % with nivolumab and 43 % with nivolumab plus ipilimumab. Increasing PD-L1 expression enhanced the efficacy of both the monotherapy and combined treatments. In patients with ≥ 50 % PD-L1 expression, ORR was 50 % with nivolumab alone and 92 % with the combination regimens. Likewise, PFS and OS where highest in the ≥ 50 % PD-L1 expression groups, although even patients without PD-L1 expression (< 1 %) derived benefit from the treatments. In those with ≥ 1 % PD-L1 expression, median PFS was 3.5 months for nivolumab monotherapy, and 10.4 months and 13.2 months for nivolumab plus ipilimumab 12-weekly and 6-weekly, respectively. At 1 year, 69 %, 91 % and 83 % of these patients were alive, respectively.

Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks is being evaluated in further studies. These include the phase III CheckMate 227 trial, which is comparing this regimen to nivolumab monotherapy, chemotherapy, and a regimen of nivolumab plus chemotherapy. The type of the comparison here depends on the PD-L1 expression levels, for which two groups have been defined (≥ 1 % and < 1 %).

Pembrolizumab plus chemotherapy: KEYNOTE-021 G

The combined use of the anti-PD-1 antibody pembrolizumab and chemotherapy as a first-line strategy for the treat-

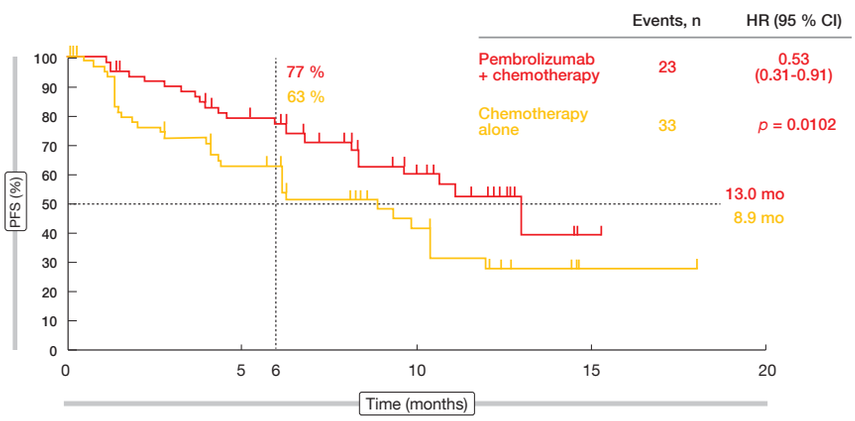


Figure 3: PFS benefit due to the addition of pembrolizumab to chemotherapy

ment of stage IIIB/IV non-squamous NSCLC was tested in the open-label, randomised, phase II KEYNOTE-021 G study. In the experimental arm, pembrolizumab was administered at a dose of 200 mg every 3 weeks for 2 years, together with carboplatin and pemetrexed. Patients in the control arm received carboplatin and pemetrexed alone over four cycles. Pemetrexed was permitted as maintenance therapy. The primary endpoint was ORR. Approximately 60 patients were treated in each arm, while 20 patients from the control arm crossed over to the pembrolizumab arm when progression set in, and 12 received anti-PD-(L)1 treatment outside of the cross-over.

The confirmed ORR was nearly double with the addition of pembrolizumab (55 % vs. 29 %; p = 0.0016) [9]. According to the PFS analysis, the combination almost halved the risk of progression or death, with median PFS exceeding 1 year (13.0 vs. 8.9 months; HR, 0.53; p = 0.0102; **Figure 3**). OS was similar between the two arms (92 % at 6 months with both treatments; 75 % and 72 % at 1 year). Pembrolizumab plus chemotherapy showed high tolerability and a manageable safety profile. As the investigators noted, pembrolizumab in combination with carboplatin and pemetrexed could be an effective treatment option for chemotherapy-naïve patients with advanced non-squamous NSCLC.

Harmonisation study on PD-L1 IHC testing in France

PD-L1 expression as assessed by IHC is the main currently available predictive biomarker for the benefit of anti-PD-1/PD-L1 antibodies. Assays used on the Dako (22C3, 28-8) and Ventana (SP142, SP263) platforms have been used as diagnostic tests in clinical trials. In France, harmonisation of assays and the development of laboratory-developed tests are urgently needed for several reasons. The Dako and Ventana platforms are not available in all pathology laboratories, and assays remain expensive, while PD-L1 testing reimbursement is insufficient to date in France. At the same time, PD-L1 testing has to be rapidly available for patients in the first-line setting, and multiple tests with different assays will not be feasible on small NSCLC samples.

A multi-centric French study therefore evaluated the analytical performance of the Dako 28-8 and 22C3, and the Ventana SP263 PD-L1 assays across various centres, with the aim of determining whether laboratory-developed tests can achieve an analytical performance close to PD-L1 assays in a set of NSCLC cases [10]. It was confirmed that the 28-8, 22C3 and SP263 assays performed in several centres showed high agreement. Among 27 laboratory-developed tests developed in seven centres on the Dako, Ventana and Leica platforms, 14 (51.8 %) were in agreement as compared to the reference assays for tumour-cell staining. Low agreement was observed for immune-cell staining when using a four-category scale with 1 %, 5 % and 10 % thresholds. Clone SP263 achieved the highest concordance rate across all of the platforms.

This study also highlights that caution is required for validation and further use of laboratory-developed tests. Selected laboratory-developed tests will be validated on larger cohorts and using external quality assessment programmes in France. These results will provide the basis for national recommendations on PD-L1 testing in NSCLC. ■

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Who is a candidate for immunotherapy?

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Which markers are available that define patients who are suitable for immunotherapy?
When we look at immunotherapy for NSCLC, we should realize that approximately 20 % of treated patients show a response. To direct treatment to patients with a higher likelihood of response, biomarkers might be of value. One biomarker that is established in clinical practice is PD-L1 expression on the tumour, according to immunohistochemistry. For the time being, there are different methodologies to assess PD-L1 expression, but they appear to coalesce slowly, so probably we will eventually have quite a reliable read-out based on immunohistochemistry. PD-L1 is not an absolute marker like the molecular aberrations that we are using for the prescription of targeted agents, but it is what is called an enrichment marker. This means that the higher the PD-L1 expression is, the higher the likelihood that the patient will respond to immunotherapy. Patients can be PD-L1–negative and still have a response, but these are only very few cases. Hence, PD-L1 expression helps to select patients for that type of expensive therapy, and it helps to select patients for immunotherapy when there are perhaps other treatment options available that might be preferable (**Figure**).

In which settings should immunotherapeutic approaches be avoided?
Immunotherapy certainly represents great progress in the treatment of NSCLC, but there are patients who are less suitable, or even who have contraindications to this type of therapy. General exclusion criteria include prior allogenic bone marrow transplantation or solid organ transplantation, as suppression of the immune system is of vital importance for those patients. Another contraindication is autoimmune disease or a history of autoimmune disease, because frequently these patients already receive immunosuppressive treatment. In these cases, stimulation of the immune system is of course not an option, and certainly not stimulation of the lymphocytes, which are often at the centre of the pathogenesis of autoimmune diseases. Furthermore, there are some other vulnerabilities that are less absolute, such as interstitial lung disease, active hepatitis, or conditions outside the autoimmune context that require systemic treatment with corticosteroids at daily doses of more than 10 mg prednisone equivalent. Cancer patients who require high doses of corticosteroids for the treatment of their brain metastases are a typical example.

How would you rate the global situation regarding practical restrictions, such as reimbursements and availability?
We have seen progress with immunotherapy in NSCLC, but most of these agents are expensive. Therefore, access to this therapy for patients is very variable across different regions of the world. In the more developed countries, we see that reimbursement for immunotherapy is gradually being implemented, but even developed nations can look very critically at the incremental value according to the incremental cost. For instance, in the United Kingdom, the national body, NICE, rejected immunotherapy for NSCLC because the cost is not in relation to the real extra value to the patient. Obviously, there is still a long way to go. We can only hope that once more agents are approved, there will be competition, which might decrease the cost of immunotherapy. This would create the possibility for access to this important therapy for an increasing number of patients and in an increasing number of countries. ■

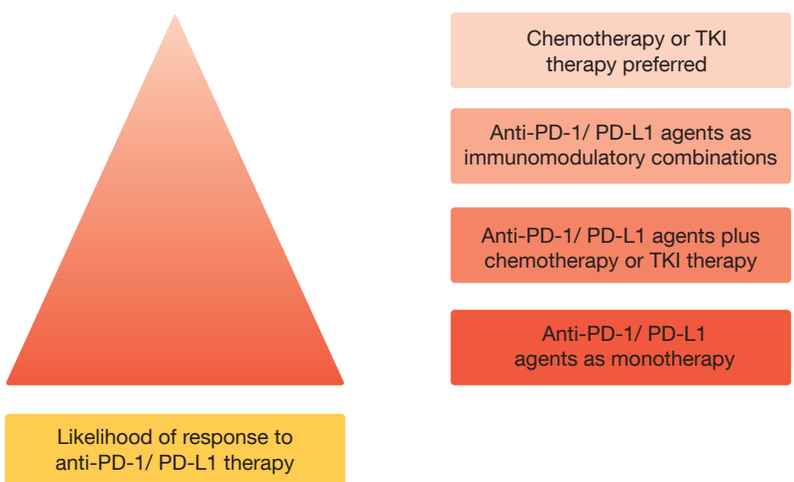

Figure: Likelihood of response to immunotherapy according to PD-L1 expression, and preferred therapeutic approaches

Anti-angiogenesis with nintedanib: activity in mesothelioma, and potential biomarkers

LUME-Meso

Malignant pleural mesothelioma generally has poor patient prognosis, as it is often diagnosed at an advanced stage. The only approved regimen consists of the combination of pemetrexed and cisplatin, which gives rise to a median OS of approximately 1 year [1]. The randomised, double-blind, placebo-controlled, phase II LUME-Meso trial tested the oral multikinase inhibitor nintedanib for treatment of mesothelioma. Nintedanib targets pro-angiogenic pathways mediated by VEGF1-3, FGFR1-3 and PDGFRα/β, as well as the kinases Src and Abl; all of these are involved in the pathogenesis of mesothelioma [2, 3]. In contrast to other drugs of the same class, nintedanib can be safely combined with commonly used chemotherapy. Nintedanib has demonstrated efficacy in *in-vitro* and *in-vivo* models of mesothelioma [4].

The LUME-Meso trial evaluated the addition of nintedanib 200 mg BID to the standard chemotherapy of pemetrexed/ cisplatin (n = 44) compared to placebo plus pemetrexed/ cisplatin alone (n = 43), in patients with unresectable malignant pleural mesothelioma who had not received prior chemotherapy. Patients who did not develop disease progression were put on nintedanib maintenance (experimental arm) or placebo maintenance (control arm) until progression. PFS was defined as the primary endpoint. This was an exploratory study, with all of the statistics intended to be descriptive.

Specific advantage in the epitheloid subtype

The addition of nintedanib to chemotherapy led to clinically meaningful PFS improvement of 3.7 months (9.4 vs. 5.7 months; HR, 0.56; p = 0.017; **Figure**) [5]. Almost all of the subgroups derived greater benefit from the combination. Nintedanib-treated patients also demonstrated improved response rate (59 % vs. 44 %) and a trend for extended OS (18.3 vs. 14.5 months; HR, 0.78), although the results are still immature here. Patients with epitheloid histology made up almost 90 % of the study population. In this group, PFS results were comparable to those in the total population, while OS showed further improvement (18.3 vs. 15.2 months; HR, 0.68), even though statistical significance was not reached.

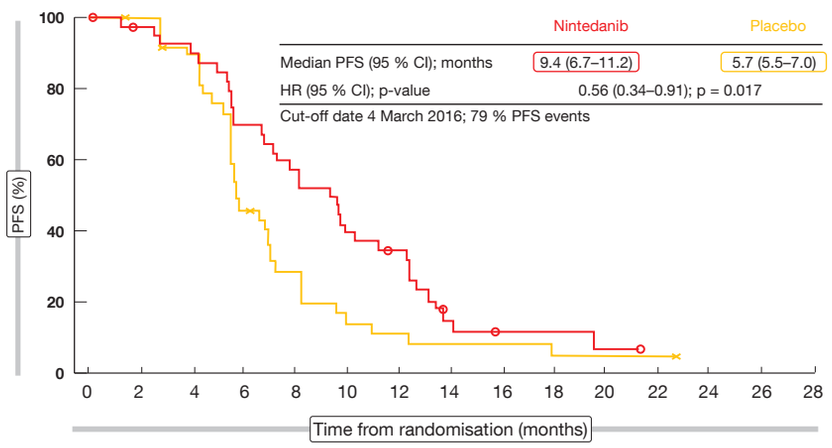

Figure: LUME-Meso: PFS with nintedanib or placebo in addition to standard chemotherapy in patients with malignant pleural mesothelioma

The safety profile was consistent with that observed in previous combination studies, and predominantly featured diarrhoea and cytopenias. Grade ≥ 3 AEs occurred only infrequently. AEs commonly reported with VEGF/ VEGFR inhibitors, such as hypertension, bleeding or thromboembolism, were rare and well balanced between the two arms. The addition of nintedanib did not decrease the number of completed chemotherapy cycles or the dose intensity of the chemotherapy. Based on these data, the phase III part of the LUME-Meso confirmatory trial is currently recruiting patients. The study design is identical with the phase II part, but only patients with epitheloid histology are being enrolled.

Angiogenic factors and radiotracer imaging

Nintedanib plus docetaxel has been approved for the treatment of adenocarcinoma of the lung after failure of chemotherapy, although not all such patients benefit from this anti-angiogenic approach. Identification of predictive markers for response is therefore vital. A phase II trial assessed the correlation between plasma levels of VEGF, FGF and PDGF and clinical endpoints of DCR, PFS and OS in patients with NSCLC treated with nintedanib plus docetaxel [6]. Thirty-eight patients diagnosed with stage IIIB/IV adenocarcinoma of the lung who had developed progression after platinum-based first-line chemotherapy were included. This is the first trial to use angiogenic factors as biomarkers for response to nintedanib therapy in patients with NSCLC. The analysis yielded promising results, as levels of angiogenic factors, particularly FGF, correlated with longer OS. Also, the development of grade 1 hypertension was associated with PFS improvement.

In the same patient population, Arrieta et al. evaluated the use of PET/ computed tomography (CT) with the peptide radiotracer [^{68}Ga]-DOTA-E-[c(RGDfK)]2 to measure the expression of αvβ3 integrin during angiogenesis in tumour tissue [7]. αvβ3 integrin is a molecular target for non-invasive monitoring of fast-growing malignant cells, as well as for assessment of treatment response. The results showed that larger baseline tumour vol-

ume was associated with longer PFS. A reduction in the percentage change (> 11.8 %) of the lung/ spleen maximum standardised uptake value index was associated with improved OS. According to the investigators, [^{68}Ga]-DOTA-E-[c(RGDfK)]2 PET/ CT appears to be a more useful tool than [^{18}F]-FDG PET/ CT for the assessment of response in NSCLC patients receiving treatment with nintedanib. ■

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Practice-changing refinements of lung cancer staging

The 8th edition of the TNM classification has recently come into effect. Compared to the 7th edition published in 2009 [1], several important adjustments have been made to lung cancer staging with the aim of improving prognostication and research [2]. "Research is of particular significance in the context of smaller tumours that can be treated with a variety of therapeutic options," said Ramón Rami-Porta, MD, PhD, Department of Thoracic Surgery, Hospital Universitari Mútua Terrassa, Terrassa, Barcelona, Spain [3]. The new edition is based on a very large number of patients, which supports its robustness [4].

Differentiation of small tumours

Changes with regard to the T descriptors account for the diversity of small tumours in the lungs, which can be identified routinely in the clinic using modern computed tomography techniques. "Tumours that had not been defined until 2011 have received names," Dr. Rami-Porta stressed. For instance, this applies to adenocarcinoma *in situ* (Tis [AIS]) and minimally invasive adenocarcinoma (T1mi). In the past, the term of 'Tis' denoted only squamous-cell carcinoma. "It is important to make a difference here, because a patient can have both," Dr. Rami-Porta explained. The smallest solid tumour, which corresponds to the new T1a category, has a maximum diameter of 1 cm **(Table 1)**.

TABLE 1
T categories according to tumour size

Descriptor	Category
≤ 1 cm	T1a
> 1-2 cm	T1b
> 2-3 cm	T1c
> 3-4 cm	T2a
> 4-5 cm	T2b
> 5-7 cm	T3
> 7 cm	T4
Bronchus < 2 cm	T2
Total atelectasis	T2
Diaphragm	T4

Awareness of smaller tumours will be raised due to the new categorisation. Also, these tumours can be used to study new treatment options, such as stereotactic radiotherapy, radiofrequency ablation, microwaves, or their combinations. Minimal resection is of interest here as well, as is the study of tumour biology in general. "Some tumours, like adenocarcinoma *in situ*, will not be resected right away, but instead be observed, allowing for the assessment of factors like growth and density."

N and M changes

For quantification of lymph node involvement, nodal stations can be used, as well as the nodal zones that were defined by the 7th edition. "There are five possibilities to quantify nodal disease based on stations," Dr. Rami-Porta said **(Table 2)**. These correspond to four prognostic groups, as patients with N1b and N2a1 have the same prognosis. The numbers of involved lymph nodes, nodal zones, and nodal stations are of importance. This is also true for the lymph node ratio, which is calculated as the ratio of involved and removed nodes. "All of this can only be assessed during pathological staging," Dr. Rami-Porta indicated.

In the area of M descriptors, the new classification states that the number of M1 lesions matters more than the location. Extrathoracic metastasis has been refined, with separation of single from multiple extrathoracic metastases in either one organ or several organs. "The sub-classification of extrathoracic metastases will contribute to a homogeneous definition of oligometastatic disease and oligoprogression, which are quite loosely defined nowadays," Dr. Rami-Porta pointed out.

Recommendations on measurement and staining

Another innovation relates to the assessment of tumour size in partially solid tumours. For computed tomography assessment, only the solid part is of interest, as it appears to be equivalent to the invasive component. The patholo-

TABLE 2
Quantification of nodal disease by number of nodal stations

N1 single	N1a
N1 multiple	N1b
N2 single N2 without concomitant N1 disease ("skip metastasis")	N2a1
N2 single N2 with concomitant N1 disease	N2a2
N2 multiple N2	N2b

gist determines the T category according to the size of the invasive component only, regardless of the size of the whole tumour, including any portions that show lepidic growth. "This innovation will change our practice," Dr. Rami-Porta emphasised. "We were used to measuring the size of the entire tumour."

Moreover, it is recommended to use elastic stains to identify invasion of the visceral pleura, which was shown to be an important prognostic factor. Dr. Rami-Porta noted that staging can change according to the extent of pleural invasion. "If this is not clear enough according to haematoxylin and eosin stains, it is important to use elastic stains." When lung cancer with multiple primary lesions is present, TNM staging is assigned to each tumour. In multiple adenocarcinomas with ground-glass opacity/ lepidic features, the highest T category is used, and the number of tumours is given in parentheses.

"The innovations in the 8th edition of TNM staging for lung cancer will increase our capacity to refine prognosis, improve tumour stratification in future trials, prompt future research, and facilitate homogeneous tumour classification, as well as collection of prospective data," Dr. Rami-Porta concluded. ■

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Inhibition of *HER2* driver mutations can confer benefits

Amplification or overexpression of *HER2* (*ErbB2*) has been identified in NSCLC, and somatic *HER2* mutations occur in approximately 2 % to 4 % of patients [1, 2]. Response to chemotherapy is poor in the setting of *HER2*-mutant advanced NSCLC [3]. Similarly, single-agent pan-HER inhibitors appear to have only limited benefit, with rare and short-lived responses [4, 5].

Neratinib plus temsirolimus

Dual pathway inhibition represents a potential treatment approach here. The HER2/ EGFR-inhibiting TKI neratinib and the mTOR inhibitor temsirolimus have synergistic effects, according to preclinical data [4] and a phase I study [5]. Therefore, an international, randomised phase II trial tested neratinib 240 mg OD with and without temsirolimus 8 mg/week in 60 patients with advanced or metastatic *HER2*-mutated NSCLC [6]. Each arm was evaluated independently, as single-agent neratinib had not been specifically assessed in lung cancer before.

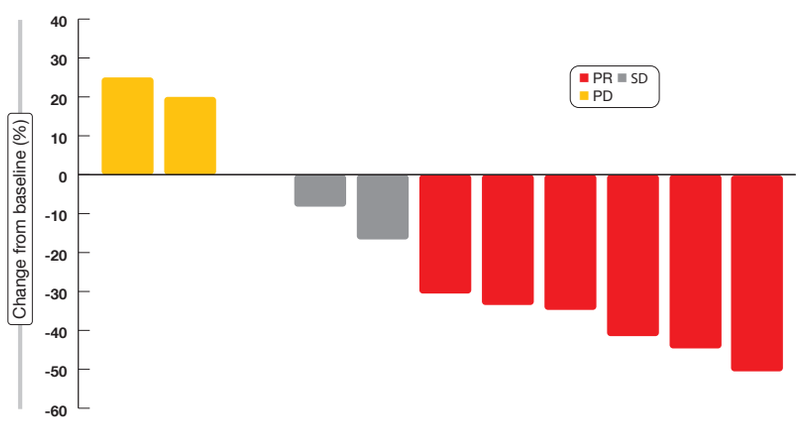

Figure: Responses to pyrotinib in 11 patients with advanced, *HER2*-positive NSCLC

This inhibition of both the HER2 and the PI3K pathways induced some activity that was superior to HER2 pathway block alone. Neratinib plus temsirolimus treatment gave rise to median PFS of 4.0 months (vs. 2.9 months with single-agent neratinib) and median OS of 15.1 months (vs. 10.0 months). Fourteen percent of the patients achieved responses with the combination (vs. 0 %). Here, one patient obtained complete remission (2 %), and five showed partial remission (12 %). The most common toxicity was diarrhoea, but this was manageable with upfront loperamide prophylaxis.

According to the analysis of the distribution of somatic *HER2* mutations and best response to therapy, mutation-specific responses did not occur; occasional responses were observed across multiple *HER2* variants. As some pa-

tients had prolonged responses of > 1 year, the search for predictive biomarkers is ongoing.

Promising results with pyrotinib

The novel oral TKI pyrotinib targets the binding of ATP to HER2 and EGFR in an irreversible manner. Encouraging preliminary findings from an open-label, single-arm phase II trial were presented at the WCLC [7]. This study assessed pyrotinib 400 mg OD in 11 patients with advanced, *HER2*-positive NSCLC after at least one chemotherapy regimen.

Partial responses were achieved in six patients (54.5 %), and three patients (27.3 %) experienced disease stabilisation **(Figure)**. The median PFS was 6.2 months, while OS had not been reached at the time of analysis, when five patients were still on treatment. Diarrhoea, fatigue and rash were the most common AEs, but all of these were grades 1 or 2. A multi-centre, large-scale phase II clinical trial will be conducted to validate these results.

Moreover, a single-arm, open-label, multi-centre phase II trial is currently testing the ErbB family blocker afatinib in patients with advanced *HER2*-mutation-positive NSCLC, as a single agent and in combination with paclitaxel after failure of platinum-based chemotherapy [8]. Afatinib has demonstrated preclinical activity in *HER2*-mutant lung cancer models and has also shown clinical activity in patients with *HER2*-mutant NSCLC [2, 9]. ■

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