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A GLOBAL CONGRESS DIGEST ON LUNG CANCER

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Editorial Board:

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Preface

Dear Colleagues,

Remarkable data in the field of lung cancer with potentially practice-changing impact have been presented at this year's ESMO Congress that took place in Madrid, Spain, from 8th to 12th September, 2017. Immunotherapeutic approaches again constituted a major topic, as clinical researchers are tirelessly exploring the multitude of conditions and limitations determining the optimal use of these drugs.

This issue of memo inOncology delineates analyses of the OAK and POPLAR trials that confirmed the activity of the PD-L1 inhibitor atezolizumab regardless of PD-L1 expression and showed that assessment of tumour mutational burden in patient blood is feasible and correlates with treatment benefits. The PD-L1 inhibitor durvalumab excelled in the PACIFIC trial in patients with stage III lung cancer, thus providing an answer to a significant unmet need. Further analyses related to the activity of the PD-1 inhibitor nivolumab in the elderly and the optimal treatment duration with nivolumab.

Likewise, immunostimulation with the toll-like receptor 9 agonist lefitolimod is a promising approach in patients with extensive-disease small-cell lung cancer. Another indication suitable for the use of immunotherapeutic agents appears to be mesothelioma, which is known to confer poor prognosis. Several analyses presented at the ESMO 2017 Congress suggested clinically meaningful benefits of various immunotherapeutic agents in patients with malignant pleural mesothelioma.

In the area of targeted therapies, the debate on sequencing of drugs is gaining momentum, as head-to-head comparisons have shown superiority of potent later-generation drugs over established first-line compounds. This is true for the EGFR tyrosine kinase inhibitor osimertinib, which outperformed gefitinib and erlotinib in *EGFR*-mutant lung cancer, as well as for the ALK inhibitor alectinib that gave rise to improvements in progression-free survival and central nervous system outcomes when compared to crizotinib in the *ALK*-positive setting. The optimal succession of agents across several treatment lines, which is crucial for the achievement of the maximum survival benefit, still needs to be determined.

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Last but not least, progress has been made with regard to targeted approaches that are under investigation for patients with rare driver mutations such as *BRAF*. When administered in a combined fashion, the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib showed substantial antitumour activity as a first-line strategy in *BRAF*-positive lung cancer patients.

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Immunotherapy: once more at the cutting edge of progress

PACIFIC: durvalumab in stage III NSCLC

Approximately one third of patients with non–small-cell lung cancer (NSCLC) presents with stage III, locally advanced disease. For those with good performance status and unresectable tumours, the standard of care is platinum-based doublet chemotherapy with concurrent radiotherapy. As no major advances have occurred in this setting over several years, there is a significant unmet need for novel therapeutic approaches to boost survival. Given the efficacy of checkpoint inhibitors in metastatic disease, the global, double-blind PACIFIC trial was initiated as the first randomised phase III study to evaluate immune checkpoint blockade in patients with stage III, locally advanced, unresectable NSCLC.

PACIFIC assessed the PD-L1 inhibitor durvalumab in patients who had not progressed following definitive platinum-based concomitant chemoradiation therapy of at least 2 cycles. They were randomised to either durvalumab 10 mg/kg every 2 weeks for up to 12 months (n = 476) or placebo (n = 237). This was an all-comer population without any restrictions regarding PD-L1 expression status. Half of the patients in each arm had squamous and non-squamous histology, respectively. The majority had obtained partial response (PR) or stable disease (SD) at the end of chemoradiation therapy. Progression-free survival (PFS) by blinded independent central review (BICR) using RECIST v1.1 and overall survival (OS) constituted the co-primary endpoint.

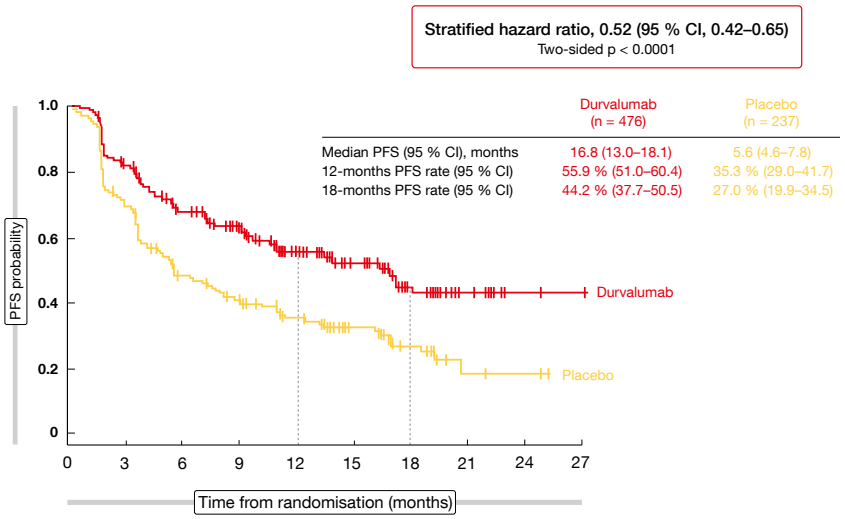

Figure 1: Progression-free survival with durvalumab vs. placebo in the PACIFIC trial

PFS difference of more than 11 months

The results of the planned interim analysis for PFS presented at the ESMO 2017 Congress after a median follow-up of 14.5 months indicated that durvalumab is a promising therapeutic option in the stage III setting [1]. As compared to placebo, durvalumab demonstrated a statistically significant and robust PFS benefit with a median improvement of more than 11 months (16.8 vs. 5.6 months; HR, 0.52; p < 0.0001; **Figure 1**). The PFS curves started to separate during the second month after treatment initiation. All pre-specified subsets benefited from the durvalumab treatment, with a similar magnitude of benefit regardless of features such as histology, best response to chemoradiation therapy, and PD-L1 expression status.

Likewise, the objective response rate (ORR) was improved in the durvalumab arm to a clinically meaningful extent (28.4 % vs. 16.0 %; p < 0.001). This also applied to the duration of response (not reached vs. 13.8 months; HR, 0.43). Accordingly, new lesions at any site, including brain metastases, developed less frequently in the experimental arm than in the placebo arm (20.4 % vs. 32.1 %), and time to distant metastasis or death by BICR was significantly prolonged (23.2 vs. 14.6 months; HR, 0.52; p < 0.0001).

Durvalumab showed a favourable safety profile that was consistent with prior reports in more advanced disease. Cough, pneumonitis, pyrexia, pneumonia, rash and hypothyroidism counted among the most frequent adverse events (AEs). No new safety signals emerged after chemoradiation treatment. For pneumonitis/ radiation pneumonitis, the difference between the durvalumab arm and the placebo arm was small (any grade, 33.9 % vs. 24.8 %). Fifteen percent compared to 10 % of patients discontinued therapy due to AEs. Immune-related AEs of any grade were observed in 24.2 % vs. 8.1 %, with low percentages of grade 3/4 events (3.4 % vs. 2.6 %). The study remains blinded to OS, as the final analysis of OS will be performed after the target number of deaths has been reached.

Confirming atezolizumab activity in PD-L1–negative patients

The randomised OAK [2] and POPLAR [3] trials showed that treatment with the anti-PD-L1 antibody atezolizumab in the second line and beyond gives rise to clinically relevant improvements in OS versus docetaxel regardless of PD-L1 expression or histology. According to the primary analysis of OAK, median OS was 13.8 and 9.6 months for atezolizumab and docetaxel, respectively (HR, 0.73; p = 0.0003) [2]. A distinct feature of the OAK results is that atezolizumab improved OS across all of the PD-L1 expression subgroups, including patients whose PD-L1 status was negative according to the SP142 assay. In this group, the HR for OS was 0.75, thus resembling the overall HR of 0.73, and median OS was 12.6 vs. 8.9 months with atezolizumab and docetaxel, respectively.

A retrospective exploratory analysis of the OAK trial confirmed that atezolizumab provides survival benefit in all patients regardless of PD-L1 status, and demonstrated improved OS in those with PD-L1-negative tumours irrespective of the assay utilised [4]. To this end, the investigators compared the two FDA-approved PD-L1 immunohistochemistry (IHC) diagnostic assays SP142 and 22C3. Tumours of 400 patients enrolled in OAK were retrospectively analysed for their PD-L1 expression using the 22C3 assay. These results were compared with the PD-L1 scores generated on the 400 tumours in the original SP142 analysis.

The investigators found that the vast majority (77 %) of SP142 PD-L1–negative patients were also PD-L1–negative according to the 22C3 assay. Atezolizumab significantly improved survival in patients with PD-L1–negative tumours according to either assay (HRs, 0.55 and 0.61 with SP142 and 22C3, respectively). Patients whose tumours were defined as PD-L1–negative by both assays showed improved OS with atezolizumab compared to docetaxel (9.9 vs. 7.7 months; HR, 0.63; p = 0.0347). This OS benefit was consistent with the overall OAK trial results.

Novel blood-based assay for tumour mutational burden

Another analysis based on the OAK and POPLAR studies demonstrated that tumour mutational burden (TMB) can be measured in blood (bTMB), and that bTMB is associated with improved PFS from immune checkpoint inhibitor therapy [5]. Gandara et al. tested a novel blood-based assay for the measurement of bTMB and evaluated the association between bTMB and atezolizumab efficacy. TMB, when measured in tumour tissue, was previously shown to correlate with atezolizumab efficacy in NSCLC [6], but as tissue is inadequate for molecular testing in approximately one third of newly diagnosed NSCLC patients, alternative sources of diagnostic material are called for.

Plasma samples from POPLAR and OAK were retrospectively assessed for bTMB using a next generation sequenc-

ing assay based on 394 genes. Two hundred eleven of 273 samples from POPLAR and 583 of 797 samples from OAK were biomarker-evaluable and constituted the biomarker-evaluable population (BEP) for the study. Circulating cell-free DNA was extracted. All base substitutions with a ≥ 0.5 % allele frequency were counted, while germline polymorphisms and predicted driver mutations were removed. In their entirety, these results constituted the bTMB score.

Enrichment for both PFS and OS was observed in the POPLAR study at several levels of bTMB, but the assay performed best at the bTMB ≥ 16 level (HR for PFS, 0.57; HR for OS, 0.56). Based on these data, bTMB ≥ 16 was selected for the confirmatory analysis in the OAK trial. The bTMB ≥ 16 population accounted for 27 % of the BEP.

Higher bBMT predicts greater PFS benefit

After there had been no overall PFS improvement in the OAK trial, the bTMB ≥ 16 subgroup showed a PFS benefit with atezolizumab compared to docetaxel. However, no prognostic effect was observed, as docetaxel-treated patients in the bTMB ≥ 16 group did not experience any PFS improvement compared to those who had bTMB < 16. For OS, the hazard ratios favouring atezolizumab over docetaxel were similar across the bTMB ≥ 16 and < 16 groups (0.64 and 0.65, respectively). This result might reflect the impact of subsequent therapies post progression, particularly in the docetaxel cohort. Median OS for the bTMB ≥ 16 subgroup was 13.5 vs. 6.8 with atezolizumab and docetaxel, respectively. An exploratory analysis found a linear increase of PFS benefits with higher bTMB cut-points (**Figure 2**). For OS, this effect was somewhat mitigated. According to an analysis of the correlation between baseline characteristics

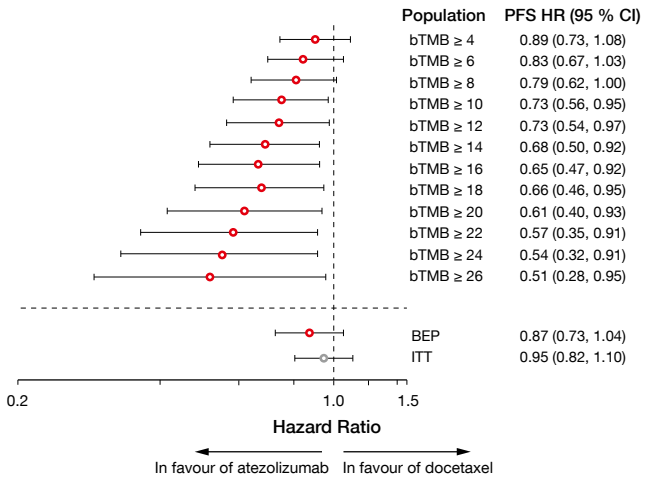

Figure 2: Incremental PFS benefit of atezolizumab with increasing bTMB cut-points in OAK

and bTMB subgroups, higher bTMB scores were associated with smoking. There was also a possible association between bTMB and clinical tumour volume, as measured by the sum of longest diameters or number of metastatic sites.

The comparison of a tissue-based TMB assay with bTMB yielded a positive percentage agreement (PPA) of 64 % and a negative percentage agreement (NPA) of 88 % (Spearman correlation, 0.59). The relatively low PPA might have been influenced by factors such as tumour heterogeneity, different computational methodologies, and different specimen acquisition times. When the same circulating tumour DNA was used, PPA and NPA were improved and supported use of the bTMB ≥ 16 cut-point. Another issue related to the potential correlation between bTMB ≥ 16 and PD-L1 expression. Here, the overlap was not significant, with only 30 patients out of 229 showing both a bTMB ≥ 16 score and the highest level of PD-L1 expression as measured by IHC.

As the authors summarised, bTMB might be particularly useful for the up to 30 % of patients who lack sufficient tissue for molecular testing. Prospective studies in the first-line setting using the bTMB assay are ongoing.

Three-year follow-up of CheckMate 017 and 057

The anti-PD-1 antibody nivolumab has been approved in many countries for the treatment of patients with advanced NSCLC and disease progression during or after chemotherapy based on the global, randomised, open-label CheckMate 017 [7] and CheckMate 057 [8] phase III trials. CheckMate 017 investigated nivolumab in patients with squamous histology, while CheckMate 057 included patients with non-squamous NSCLC. Both trials showed significantly improved OS and a favourable safety profile in the nivolumab arm as compared to docetaxel. Felip et al. presented the updated efficacy and safety data from CheckMate 017 and CheckMate 057 based on at least three years of follow-up [9].

Nivolumab continued to demonstrate long-term benefits, with the OS and PFS curves plateauing in both trials. The 3-year OS rates in CheckMate 017 were 16 % *versus* 6 % with nivolumab

TABLE 1
Tumour responses in CheckMate 017 and CheckMate 057 after a minimum follow-up of 3 years

	CheckMate 017		CheckMate 057	
	Nivolumab (n = 135)	Docetaxel (n = 137)	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR, %	20	9	19	12
Median duration of response, months	25.2	8.4	18.3	5.6
Response ongoing, n/N (%)	7/27 (26)	0/12 (0)	13/56 (23)	0/36 (0)

and docetaxel, respectively. In CheckMate 057, these were 18 % *versus* 9 %. As is known, PD-L1 expression predicted the OS benefit in the non-squamous group included in CheckMate 057, while this effect was less pronounced in the CheckMate 017 population with squamous histology. Three-year PFS rates were 12 % *versus* not calculable in CheckMate 017, and 10 % *versus* < 1 % in CheckMate 057.

Among responders, patients treated with nivolumab experienced longer median duration of response than those in the docetaxel arm. Twenty-six percent and 23 % of patients in CheckMate 017 and CheckMate 057, respectively, who responded to nivolumab, had ongoing tumour responses (**Table 1**). No ongoing responses were observed in the docetaxel arms of the two trials. The long-term follow-up showed no new safety signals for nivolumab, and rates of treatment-related AEs were similar to those seen in the past.

Data on nivolumab in the elderly

Preliminary results from the large ongoing CheckMate 171 study support nivolumab as a therapeutic option in previously treated patients with advanced, squamous NSCLC, including those aged ≥ 70 years or with an ECOG performance status (PS) of 2 [10]. Most lung cancer patients are diagnosed at an advanced age and therefore frequently present with comorbidities. However, data on therapeutic options in these patients are limited, as they are usually under-represented in randomised clinical trials. The single-arm, phase II CheckMate 171 study is exploring safety and survival outcomes in heavily pre-treated patients (n = 809) who received nivolumab monotherapy after progression on platinum-based chemotherapy, including patients aged ≥ 70 years (n = 279) and those with ECOG PS 2 (n = 98).

The analysis showed that estimated median OS as well as OS rates at 3 and 6 months were comparable across the overall population and patients aged ≥ 70 years (**Table 2**). Patients with ECOG PS 2 experienced slightly poorer results. PR rates at week 9 were 14 %, 14 % and 11 % for the overall population, patients aged ≥ 70 years, and those with ECOG PS 2, respectively. The safety profile of nivolumab was comparable across these three groups, including rates of grade 3/4 treatment-related AEs, all-grade AEs, and AEs leading to discontinuation.

TABLE 2
Overall survival obtained with nivolumab in all patients, those aged ≥ 70 years, and those with ECOG performance status 2

	All patients (n = 809)	Patients aged ≥ 70 years (n = 279)	Patients with ECOG PS 2 (n = 98)
Median OS, months	9.9	11.2	5.4
3-month OS rate, %	81	78	65
6-month OS rate, %	67	66	46

How long should nivolumab be administered?

Optimal duration of treatment with PD-(L)1 inhibitors remains an important question. While the majority of nivolumab data are based on treatment until disease progression or unacceptable toxicity, findings from the phase I CheckMate 003 study suggest that approximately two years of nivolumab monotherapy are sufficient for long-term clinical benefit in patients with previously treated NSCLC [11]. CheckMate 153 was the first randomised study to evaluate duration of treatment with a PD-(L)1 inhibitor [12]. It compared continuous administration of nivolumab *versus* nivolumab treatment limited to one year. Patients with advanced or metastatic NSCLC of squamous or non-squamous histology who had at least one prior systemic therapy were eligible. ECOG performance status of 0-2 was allowed, as well as treated CNS metastases. This was a heavily pre-treated cohort; a quarter in each arm had received at least three prior therapies, and one third had received two therapies.

All of the patients (n = 220) underwent treatment with the standard dose of nivolumab (3 mg/kg every 2 weeks) for one year. After that, they were randomised to either continuous nivolumab or treatment discontinuation, with the opportunity to receive re-treatment at progression. Only patients who had achieved disease control (i.e., complete response [CR], PR, SD) at the time of randomisation were included in the efficacy analysis. This applied to 76 patients in the continuous arm and 87 in the discontinuation arm.

Findings support continuous treatment

Within this group, patients derived significantly greater benefit from continuous nivolumab with respect to PFS from randomisation (not reached vs. 10.3 months; HR, 0.42; **Figure 3**). At one year, PFS rates were 65 % vs. 40 %. Furthermore, continuous nivolumab showed greater activity independent of

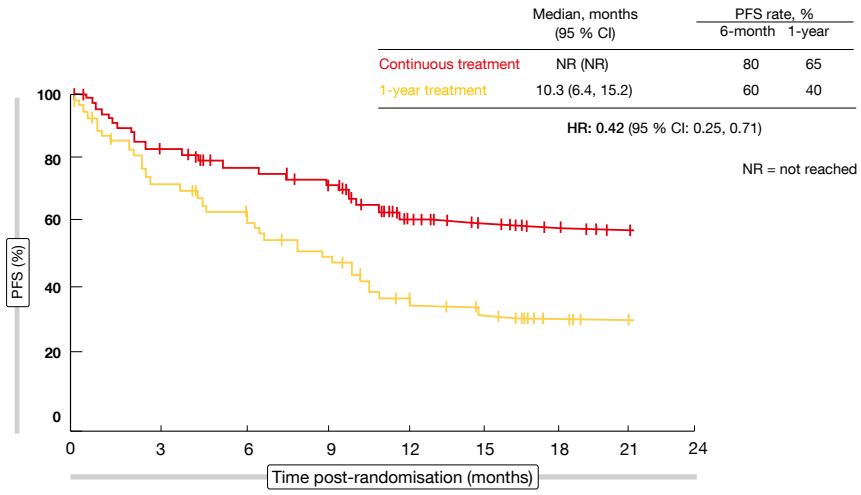

Figure 3: Continuous nivolumab administration vs. discontinuation after 1 year: progression-free survival

response status at the time of randomisation: for patients with CR or PR, median PFS was not reached vs. 10.6 months (HR, 0.45), and for those with SD, not reached vs. 9.6 months (HR, 0.44). The multivariate analysis favoured continuous nivolumab (HR, 0.43) even after adjustment for gender, histology, best overall response, and PD-L1 status. OS was longer for continuous nivolumab, although not to a statistically significant extent.

Among patients who were randomised to treatment discontinuation, 43 experienced disease progression thereafter. Thirty-four of these were retreated with nivolumab. Median duration of retreatment was 3.8 months (range, 0.1–17.5 months). Most patients showed increases in target lesion size, although some experienced treatment benefits. Regarding safety after randomisation, there was a generally higher incidence of treatment-related (serious) AEs in the continuous treatment arm compared to the 1-year treatment arm. Few new-onset events occurred after one year. No treatment-related deaths were reported in either of the trial arms, and no new safety signals emerged in the overall cohort.

Updated results of KEYNOTE-021

Cohort G of the KEYNOTE-021 study was an open-label, randomised phase II trial investigating the combination of the anti-PD-1 antibody pembrolizumab with pemetrexed/ carboplatin chemotherapy compared to pemetrexed/ carboplatin alone. Patients with previously untreated advanced non-squamous NSCLC were enrolled. According to the primary analysis conducted after a median follow-up of 10.6 months, the pembrolizumab-based combination conferred significant improvements with regard to ORR (55 % vs. 29 %; p = 0.0016) and PFS (HR, 0.53; p = 0.010) [13]. At that time, HR for OS was 0.90. An updated analysis presented at the ASCO Congress 2017 showed that the ORR and PFS benefits were maintained, while the mortality risk had decreased (HR for OS, 0.69; p = 0.13) [14]. Both the primary and secondary analysis yielded a manageable safety profile of the combination.

At the ESMO 2017 Congress, Borghaei et al. presented updated findings after a median follow-up of 18.7 months [15]. Again, the significant improvements in ORR and PFS were maintained. ORR was 56.7 % vs. 31.7 %. As compared with the pre-specified analysis, three additional responses had been observed, one in the experimental arm and two in the control arm. In each group, one CR had developed. Median duration of response in either arm had not been reached; 50 % vs. 40 % of patients showed ongoing responses. PFS for the pembrolizumab and chemotherapy-only arms was 19.0 vs. 8.9 months, respectively (HR, 0.54). For OS, the incremental benefit continued to increase (HR, 0.59) despite the substantial proportion of patients in the control arm who had received anti-PD-(L)1 treatment inside and outside of the crossover (63 % of the intent-to-treat population). However, the OS difference was not statistically significant due to low patient numbers.

Likewise, changes in toxicity compared to the last update were limited. One additional AE had led to treatment discontinuation in each arm. Toxicity profiles were as anticipated. No grade 5 AEs with possible immune aetiology had occurred.

Prevalence and impact of hyper-progression

Hyper-progressive disease (HPD) in the context of immunotherapy has been described in 9 % of 131 advanced cancer patients treated with immunotherapy in early phase trials [16]. Lahmar et al. reported increases of > 50 % of tumour volume in 10 % of 89 NSCLC patients [17]. A retrospective study conducted at five French institutions assessed the prevalence of HPD, its prognostic value and its correlation with clinical characteristics in a large cohort of patients with advanced NSCLC who received immunotherapy [18]. Two CT scans were required before the start of immu-

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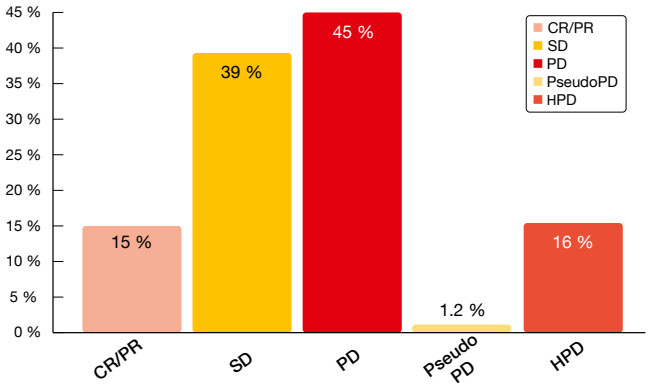
notherapy and one during treatment; the interval between the baseline CT scan and the start of treatment had to be ≤ 6 weeks. CT scans were centrally assessed according to RECIST 1.1. Of 365 screened patients, 242 (66 %) were included.

According to this analysis, the administration of immunotherapy accelerated tumour growth in 36 % of patients, while 64 % showed either regression or SD. In 40 cases (16 %), HPD occurred (**Figure 4**), which was defined as a > 50 % difference across the tumour growth rates before and after treatment initiation. Pseudo-progression took place in 1.2 %.

The analysis of clinical characteristics according to progression status yielded increased risk for HPD in the presence of more than two metastatic sites before the start of treatment. HPD was identified as a negative prognostic factor: for patients experiencing progression that was not HPD, median OS was 5.7 months, whereas those developing HPD showed a median OS of only 3.3 months (HR, 0.39; p = 0.011). ■



CR/ PR, complete response/ partial response; SD, stable disease; PD, progressive disease; PseudoPD, pseudo-progression; HPD, hyper-progressive disease

Figure 4: Response patterns in immunotherapy-treated lung cancer patients

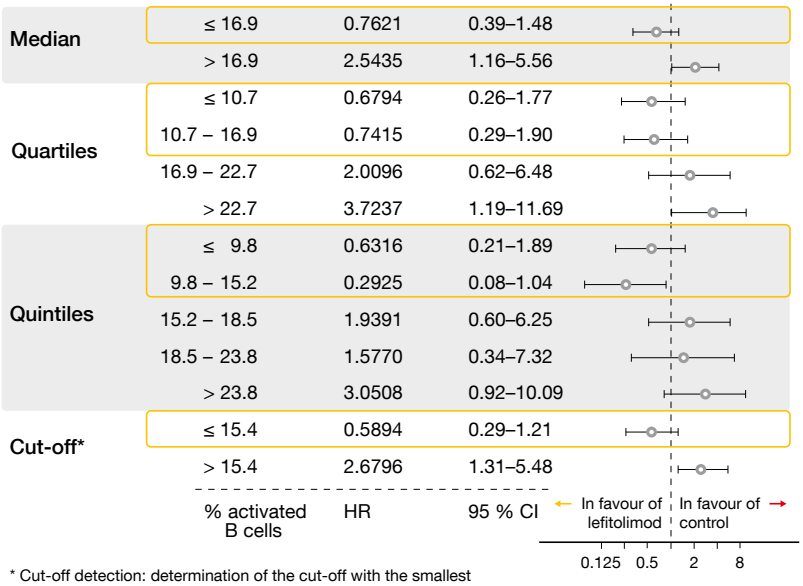
Immunostimulation as a promising approach in SCLC

IMPULSE

There is a high unmet medical need regarding extensive-disease small-cell lung cancer (SCLC) that shows poor outcomes with median OS of 9 to 11 months. First-line chemotherapy usually evokes marked responses, but responders typically experience only limited periods of disease control.

Based on the hypothesis that activation of the immune system might prolong disease stability in these patients, thus ultimately affecting their survival, Thomas et al. assessed the activity of the toll-like receptor 9 (TLR9) agonist lefitolimod [1]. Lefitolimod initiates immune surveillance by broad enhancement of the innate and adaptive immune system via multiple pathways, taking advantage of the decreased tumour burden and released tumour antigens during chemotherapy [2–4].

The exploratory, randomised, controlled, phase II IMPULSE study took place at 41 centres in Belgium, Austria, Germany and Spain. Patients with extensive-disease SCLC who had already developed PR or CR after four cycles of platinum-based induction chemotherapy were enrolled. They were randomised in a 3:2 ratio either to the experimental group (n = 61) that was treated with lefitolimod plus platinum-based chemotherapy (5th/ 6th cycle) followed by lefitolimod maintenance, or to the control group (n = 41). Here, patients only received the 5th/ 6th cycle of



* Cut-off detection: determination of the cut-off with the smallest p value in a univariate Cox regression model (without treatment)

Figure: Overall survival in patients with low counts of activated B cells across different analyses

chemotherapy followed by subsequent treatment according to local practice. Lefitolimod was administered at a dose of 60 mg subcutaneously twice weekly. OS in the intent-to-treat (ITT) population was defined as the primary endpoint of the IMPULSE study.

Confirmation of the mode of action

A selected secondary endpoint of the trial consisted in the standardised detection of pharmacodynamic markers (i.e., activation of monocytes and secretion of the chemokine IP-10) to confirm the mode of action of lefitolimod. Monocytes and IP-10 were assessed in a comparative manner before the initiation of treatment and at least 4 weeks thereafter. Indeed, significant increases of CD169-positive monocyte counts and IP-10 levels occurred as expected. IMPULSE demonstrated limited add-on toxicity of lefitolimod in combination with chemotherapy. Cough and headache preponderated in the experimental arm compared to the control arm. Grade 3 AEs occurred only infrequently, and no grade 4 or 5 AEs were reported.

Although the OS analysis of the ITT population revealed no significant difference in survival (279.0 vs. 272.0 days with the lefitolimod-based regimen and chemotherapy only, respectively; HR, 1.27; p = 0.53), there were signals of activity of lefitolimod in certain subgroups according to pre-planned analyses. Patients with reported chronic obstructive pulmonary disease (COPD) experienced a 46 % reduction in their mortality risk (316.0 vs. 246.0 days; HR, 0.54).

Activity in the presence of low activated B cell counts

Interesting results were obtained for the population with low numbers of activated B cells at baseline. This cohort comprised 38 individuals, 23 of whom received lefitolimod. Median OS was 284.0 vs. 231.5 days with lefitolimod and chemotherapy only for these patients (HR, 0.59). Activated B cells were defined as the CD86-positive proportion of CD19-positive B cells, with a cut-off at 15.4 %. The predictive value of low activated B cell counts persisted across different analyses (i.e., median, quartiles, quintiles, delineated cut-off; **Figure**).

This phenomenon might be due to suppression of the lefitolimod-triggered anti-tumour response by activated/ regulatory B cells, which implies that low numbers of these cells facilitate the full effect of lefitolimod treatment. Next steps include the validation of lefitolimod in a patient population with low counts of activated B cells. ■

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Randomised findings on CT-based follow-up after resection of early NSCLC

Regarding the optimal follow-up after surgery for early-stage NSCLC, the ESMO guidelines recommend patient surveillance every six months for 2-3 years with visits including history, physical examination and preferably contrast-enhanced spiral chest CT at 12 and 24 months [1]. Thereafter, annual visits including history, physical examination and chest CT should be performed to detect second primary tumours (SPCs). However, these recommendations are not based on randomised trials and therefore only have a low-to-moderate level of evidence.

The multi-centre phase III IFCT-0302 trial was the first large randomised study on follow-up after surgery for NSCLC and the first randomised trial to evaluate the interest of chest CT [2]. It compared minimal follow-up (Min), consisting of clinical visits with history and physical examination, chest x-ray and CT scan only in case of symptoms or abnormal chest x-ray, with maximal follow-up (Max). Max included history and physical examination as well as chest x-ray, but also contrast-enhanced CT scan of the thorax and upper abdomen. Fiberoptic bronchoscopy was mandatory for squamous and large-cell carcinomas.

In both arms, patients completed follow-up every six months for two years, followed by annual visits. A total of 1,775 patients with clinical stage I, II, or IIIA and T4 N0-2 NSCLC were enrolled within eight weeks after anatomic complete resection. Overall survival was defined as the primary endpoint.

After a median follow-up of 8 years and 10 months, OS did not differ significantly between the two arms (123.6 and 99.7 months with Max and Min, respectively; HR, 0.94; p = 0.37). At eight years, 54.6 % vs. 51.7 % of patients were alive. There was a trend for a shorter disease-free survival in the Max cohort (59.2 months vs. not reached; p = 0.07), which reflects earlier detection of recurrence and SPCs by CT scan. According to an exploratory analysis, patients experiencing relapses or SPCs at 24 months achieved the same median OS with both surveillance strategies, whereas CT-based surveillance significantly improved OS in those without recurrence or SPCs at 24 months.

The authors concluded that CT scans every six months are probably of no value during the first two years after surgery, but annual chest scans might be useful in the long term. Patients at high risk for SPCs that are potentially amenable to curative treatment can experience long-term benefits. ■

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EGFR-mutant lung cancer: sequencing as a major topic in light of new data

Long-term results with osimertinib after EGFR TKI failure

The first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) erlotinib and gefitinib as well as the second-generation EGFR TKI afatinib are the recommended first-line options for patients with *EGFR*-mutant NSCLC [1]. Regardless of the extent of initial response, however, more than 60 % of patients develop the T790M resistance mutation [2]. The third-generation EGFR TKI osimertinib, which is selective for both activating *EGFR* mutations and *EGFR* T790M resistance mutations, has recently been approved in the USA and Europe for the treatment of patients with advanced, T790M-positive NSCLC. In the two pivotal phase II AURA extension and AURA2 studies, patients with T790M-positive NSCLC following disease progression on prior EGFR TKI treatment benefited from osimertinib therapy with regard to ORR and PFS [2, 3].

At the ESMO 2017 Congress, Mitsudomi et al. reported long-term follow-up and OS data from the pooled analysis of the AURA extension and AURA2 trials [4]. A total of 411 patients had received osimertinib 80 mg/d until progression or study discontinuation. At the time of data cut-off, median duration of osimertinib treatment was 16.4 months. Median OS and PFS were 26.8 and 9.9 months, respectively, and ORR was 66 %. Median duration of response amounted to 12.3 months. Forty-one percent of patients had new lesions by investigator assessment at data cut-off, the most common sites being lung (13 %), CNS (8 %), bone (7 %) and liver (7 %).

Of 301 patients who progressed on osimertinib, 221 (73 %) continued treatment with a median treatment duration of 4.4 months. After discontinuation of osimertinib, 69 % of patients received other anti-cancer therapies. This analysis also confirmed the manageable safety profile of osimertinib, with very low rates of grade ≥ 3 AEs. In total, 4 % of patients discontinued treatment due to possibly causally related AEs.

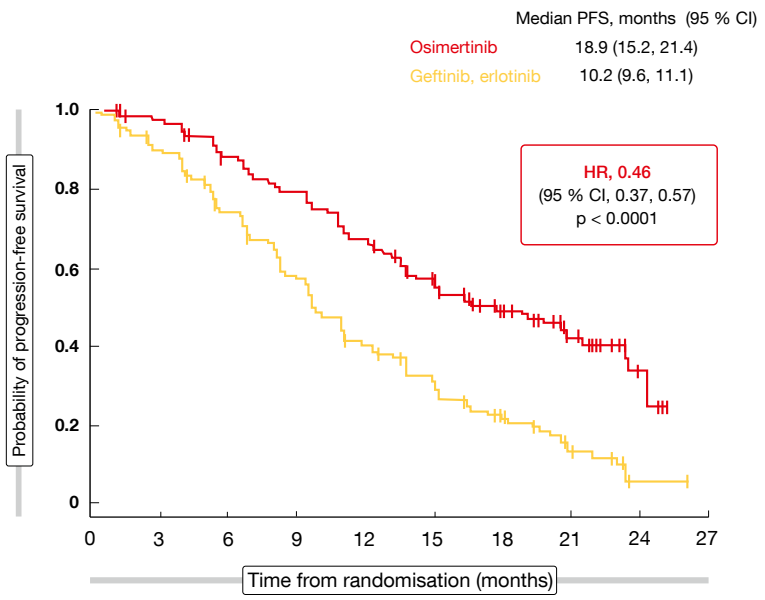

Figure 1: Primary endpoint of the FLAURA study: progression-free survival with osimertinib vs. gefitinib and erlotinib

FLAURA: first-line osimertinib

After osimertinib had been established as an effective treatment option in the T790M-mutated lung cancer setting, the FLAURA trial evaluated the first-line use of this agent in patients with advanced NSCLC harbouring activating *EGFR* mutations (i.e., exon 19 deletion or L858R mutation) [5]. FLAURA had a double-blind, placebo-controlled, randomised phase III design. In the experimental arm, 279 patients received osimertinib 80 mg/d, while medication in the control arm (n = 277) consisted of either gefitinib 250 mg/d or erlotinib 150 mg/d. Two thirds of control patients were treated with gefitinib. The enrolment of patients with stable central nervous system (CNS) metastases was allowed, as well as crossover to open-label osimertinib upon central confirmation of disease progression and T790M positivity. PFS according to RECIST 1.1 based on investigator assessment constituted the primary endpoint.

Compared to the control group, the osimertinib-treated arm experienced a significant improvement in PFS (18.9 vs. 10.2 months; HR, 0.46; p < 0.0001; **Figure 1**) that represented a 54 % reduction in the risk of progression or death. The PFS curves separately early on and remained separated throughout the course of treatment. All of the subgroups derived more favourable PFS outcomes from osimertinib treatment than from the first-generation EGFR TKIs.

Doubling of duration of response

The analysis according to the presence of brain metastasis at baseline showed a consistent PFS benefit across the entire cohort: for patients with CNS metastases, PFS was 15.2 vs. 9.6 months (HR, 0.47; p = 0.0009), and for those without CNS metastases, 19.1 vs. 10.9 months (HR, 0.46, p < 0.0001). CNS progression events occurred in 6 % vs. 15 % in the whole group.

Objective response rates did not differ significantly between the two arms (80 % vs. 76 %; p = 0.2335), but osimertinib gave rise to a doubling of the dura-

tion of response (17.2 vs. 8.5 months). At the time of the analysis, median OS had not been reached in either arm, although the curves hinted at an advantage of osimertinib (HR, 0.63). The p value equalled 0.0068; at current maturity, a p value of < 0.0015 was required for statistical significance as determined by the O'Brien-Fleming approach.

The safety profile of osimertinib was comparable to the safety profiles of gefitinib and erlotinib, although with lower rates of grade ≥ 3 AEs (34 % vs. 45 % for osimertinib and gefitinib/ erlotinib, respectively) and a lower discontinuation rate (13 % vs. 18 %). Stomatitis occurred slightly more often with osimertinib, whereas acneiform dermatitis and elevations of transaminases showed comparably lower rates. Based on these results, the authors concluded that osimertinib is a new standard of care for first-line therapy of patients with *EGFR*-mutant advanced NSCLC.

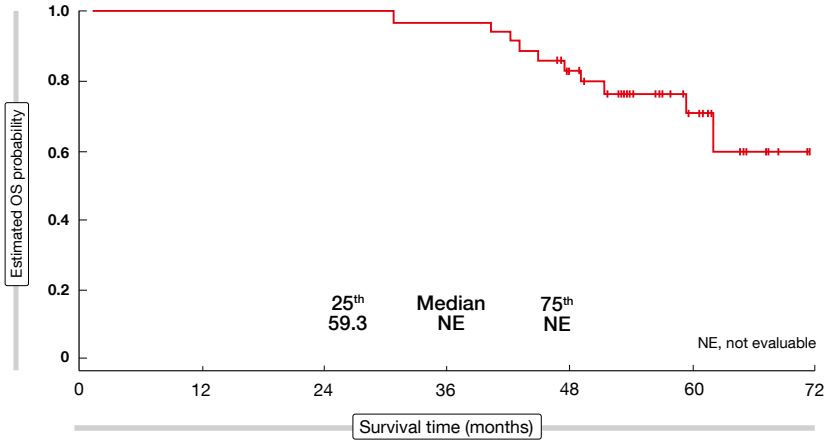

Figure 2: Exploratory analysis of survival in patients starting on afatinib treatment who received subsequent osimertinib in any line

Criticism of FLAURA

In his discussion of the results of the FLAURA trial, Tony Mok, MD, Chinese University of Hongkong, China, pointed out that FLAURA is undoubtedly a positive study showing a significant benefit of first-line osimertinib, but posed the question of whether all *EGFR*-mutation–positive patients should indeed receive first-line osimertinib [6]. Several shortcomings of the trial design are calling for caution. For one, afatinib was not used as a comparator despite being a standard of care. Moreover, FLAURA did not clearly demonstrate the CNS activity of osimertinib, as the PFS advantage observed in patients who presented with brain metastases at baseline reflects systemic PFS rather than intracranial PFS. The presence of CNS lesions was not a stratification factor, which led to a slight imbalance in prevalence between the two groups (19 % and 23 % in the osimertinib and control arms, respectively), and CNS imaging was not mandatory for all patients. Thus, researchers did not assess intracranial CNS response in a prospective fashion. In addition, results obtained with gefitinib and erlotinib were pooled in the control arm, even though their CNS penetration rates are known to be different.

As Dr. Mok noted, the ultimate goal of lung cancer treatment is OS prolongation by optimal sequencing of effective agents. Survival in both arms of the FLAURA trial remains uncertain, as OS data for osimertinib are immature and 64 patients in the control arm are still receiving either gefitinib or erlotinib, which means that they might switch to osimertinib later on. The impact of the crossover to osimertinib is not reflected, as only 62 out of 213 patients who progressed received second-line osimertinib to date. Finally, resistance mechanisms and potential treatment strategies for patients who have failed first-line osimertinib treatment are currently unclear. Various targetable mutations are under investigation, but effective treatments still need to be established.

Data on sequencing from the LUX-Lung trials

In the phase III LUX-Lung 3 and 6 studies, treatment-naïve patients with stage IIIB/IV *EGFR*-mutant NSCLC were randomised to either afatinib or platinum-doublet chemotherapy [7, 8]. Compared to chemotherapy, afatinib significantly

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improved PFS and ORR in these trials. OS was significantly prolonged in the subgroup whose tumours had deletion 19 [9]. Patients included in the phase IIb LUX-Lung 7 trial, on the other hand, received either afatinib or gefitinib in a randomised manner. They significantly benefited from afatinib with regard to PFS, time to treatment failure, and ORR [10]. No OS difference was observed between the two arms [11].

Sequist et al. conducted a retrospective analysis of subsequent therapy outcomes in patients with common *EGFR* mutations in LUX-Lung 3, 6 and 7, with the aim of contributing to establishing the optimal treatment sequence for patients with *EGFR*-mutant NSCLC [12]. Among 579 patients with common mutations randomised to afatinib, 553 had discontinued afatinib treatment at the time of analysis. Seventy-one percent of these received subsequent any-line treatment, which was mostly platinum-based chemotherapy (50 %), first-generation TKI monotherapy (34 %), single-agent chemotherapy (33 %), or other treatments (22 %). The proportion of patients treated with subsequent therapies is similar to that observed in trials of other EGFR TKIs [13, 14]. There was no relevant difference in treatment duration across deletion 19 and L858R *EGFR* mutational subgroups.

A total of 37 patients who discontinued afatinib received subsequent osimertinib, mostly in the third-line setting and beyond. For these patients, median time on osimertinib in any treatment line was long at 20.2 months, and after a median follow-up of more than 4 years, OS had not yet been reached **(Figure 2)**.

According to the authors, these encouraging outcomes suggest that further investigation of this treatment sequence in a larger cohort is warranted. Overall, these findings support treatment sequencing with first-line afatinib followed by subsequent therapies, including osimertinib. ■

Interview: Nicolas Girard, MD, PhD; Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France

Survival is the result of multiple treatment lines

To what extent will the data of the FLAURA trial that explored first-line use of osimertinib in patients with *EGFR*-mutated advanced NSCLC change clinical practice?

FLAURA is a positive trial, as its results favour osimertinib over gefitinib and erlotinib. Now we have to consider this among the multiple options that are available for the first-line treatment of *EGFR*-mutant lung cancer. Besides osimertinib, there are the first-generation TKIs erlotinib and gefitinib and the second-generation TKI afatinib, but maybe sometime soon also dacomitinib, for which data were presented at the last ASCO Meeting [1].

Before starting treatment for a patient with *EGFR*-mutant lung cancer, it is necessary to consider the global sequence. We need to look at subsequent treatment options, including chemotherapy and other options, and to think about resistance mechanisms. It is important to understand what the best sequence for each patient is. Is it osimertinib upfront, or is it the sequence of first-generation or second-generation TKIs followed by osimertinib, based on the AURA3 data [2]?

How does sequencing of different EGFR-directed agents affect survival?

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The ultimate objective of the anti-EGFR treatment sequence is improvement in survival. We clearly need to increase PFS, but I think that the median PFS results of first-line and second-line treatment do not necessarily add up to the actual OS of the patient. At this congress, Dr. Sequist et al. reported on subsequent treatments after afatinib in the LUX-Lung 3, 6 and 7 trials, showing that the OS of patients was far longer than the sum of median PFS results after several lines of treatment [3]. Clearly, there is an impact of the previous treatment on the effect of the subsequent therapy. This is mostly driven by tumour biology and by the emergence of the T790M resistance mutation, but possibly also by other resistance mechanisms to osimertinib that have not been identified yet.

What are the consequences for clinical practice?

We clearly need more data on sequencing of drugs in clinical trials. In addition, in order to guide our clinical decisions, we need to have a close clinical and radiological follow-up of patients, but also a molecular follow-up. One point is safety. We are aware that side effects might occur more frequently with second-generation TKIs, although after 10 years of experience with EGFR TKIs, we know how to prevent and manage these side effects. However, this is a factor to consider with respect to the global patient quality of life. ■

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Reaching unprecedented outcome dimensions in malignant mesothelioma

Malignant pleural mesothelioma (MPM) is a rare but aggressive cancer with poor prognosis. While combination chemotherapy with platinum and pemetrexed with or without bevacizumab is a standard in first-line treatment, no approved second-line strategies have been established to date [1]. Gemcitabine or vinorelbine are often used in this situation, but these only show limited activity [2].

However, there is a strong rationale for the assessment of immunotherapy in patients with MPM. The inflammatory phenotype of these tumours hints at the involvement of T cells, and MPM cells express PD-L1 in a substantial proportion of cases [3-6]. Moreover, PD-L1 expression has been correlated with worse prognosis in MPM [7, 8].

MAPS2: combination immunotherapy

The randomised, non-comparative phase II MAPS-2 trial independently evaluated nivolumab 3 mg/kg every 2 weeks (n = 63) and the combination of nivolumab with the anti-CTLA-4 antibody ipilimumab 1 mg/kg every 6 weeks (n = 62) until disease progression or toxicity, for a maximum of 2 years. Patients with unresectable MPM and documented progression after one or two lines of chemotherapy including a pemetrexed/platinum doublet were enrolled. In each arm, PD-L1 expression status was available in 79 % of patients.

The disease control rate (DCR) at 12 weeks was defined as the primary endpoint based on the statistical plan and was met in both arms. Among the first 108 eligible patients, 50.0 % and 44.4 % treated with the combination and nivolumab monotherapy, respectively, experienced disease control at 12 weeks, as previously reported [9]. In the ITT population, DCRs amounted to 51.6 % and 39.7 %, respectively. These are meaningful increases compared to historical data and previous non-immunotherapy clinical trials.

TABLE
Association between PD-L1 expression and response in MAPS2 (pooled analysis of patients treated with nivolumab and nivolumab plus ipilimumab)

	Negative (n = 58)	Positive ≥ 1 % (n = 41)	p value
Objective response	12.1 % (n = 7)	39.0 % (n = 16)	0.003
Disease control	41.4 % (n = 24)	53.7 % (n = 22)	0.26
	Negative (n = 92)	**Positive ≥ 25 % (n = 7)**	**p value**
Objective response	19.6 % (n = 18)	71.4 % (n = 5)	0.007
Disease control	43.5 % (n = 40)	85.7 % (n = 6)	0.047
Progression	44.6 % (n = 41)	14.3 % (n = 1)	0.23

Zalcman et al. presented updated findings from the MAPS-2 trial at the ESMO 2017 Congress [10]. According to a pooled analysis of patients with available PD-L1 status, PD-L1 expression ≥ 1 % significantly correlated with response, and high PD-L1 expression (≥ 25 %) correlated with both objective response and disease control **(Table)**. Median duration of response was 7.9 and 7.4 months, respectively. Long-lasting remissions were observed for all histological subtypes (i.e., epithelioid, biphasic, sarcomatoid).

Extension of median survival beyond 15 months

After a median follow-up of 15 months, median OS was not reached and 13.6 months in the combination and monotherapy arms, respectively. As in the most recent analysis [9], PFS for nivolumab plus ipilimumab and nivolumab alone was 5.6 and 4.0 months, respectively, after the extended follow-up showing the maturity of such analyses. The exploratory forest plot showed that patients with sarcomatoid/biphasic histology fared better regarding OS when they were treated with the combination, while they did worse with nivolumab monotherapy. This also applied to those who received immunotherapy in the third *versus* second line. Conversely, patients with PD-L1 expression (≥ 1 % vs. < 1 %) benefited from nivolumab, while both subsets benefited equally from nivolumab plus ipilimumab. The greatest benefit from nivolumab only occurred in patients who had progressed more than 3 months after pemetrexed therapy (HR, 0.25; p = 0.002). Due to small patient numbers, these results are only hypothesis-generating, however.

Toxicity of the regimens assessed was generally manageable. Grade 3 AEs occurred more frequently with the combination, although not to a significant degree (22.9 % vs. 12.7 %). With nivolumab plus ipilimumab, two patients experienced grade 4 AEs, and there were three deaths deemed treatment-related, occurring early in the trial course, due to fulminant hepatitis, encephalitis, and acute kidney failure. None of the patients receiving nivolumab monotherapy had grade 4/5 AEs. Patients in the combination arm reported more frequently diarrhoea, pruritus, and dry skin. For the majority of documented immune-related AEs, higher rates were noted with nivolumab plus ipilimumab, but most of these were grades 1 and 2.

Quality of life assessments at 12 weeks favoured nivolumab monotherapy for global, pain, anorexia and interference items, although not significantly. On the other hand, patients treated with the combination reported advantages regarding the general item and symptom distress scales. Long-term and longitudinal quality-of-life studies are pending. As the authors concluded, the results of MAPS-2 support

the recent NCCN panel decision to recommend the monotherapy or the combination therapy as options for the second or third line in relapsing MPM patients.

Activity of pembrolizumab in a Swiss registry

Early phase trials investigating the anti-PD-1 antibody pembrolizumab in patients with mesothelioma have yielded promising outcomes. In the KEYNOTE-028 study, DCR was 72 %, and median OS amounted to 18 months [11]. The Chicago cohort showed a DCR of 80 % and a median OS of 11.9 months [12]. Based on these trials, pembrolizumab started to be used for the off-label treatment of relapsed MPM in Switzerland. The aim of the Swiss registry was to assess the activity of pembrolizumab in relapsed MPM in a real-life setting. Thirteen cancer centres in Switzerland contributed their data. PD-L1 quantification was performed in a central laboratory, whereas local investigators determined clinical responses.

According to a retrospective analysis of the registry, 48 patients with a median age of 68.5 years at diagnosis were included until April 2017 [13]. The majority (73 %) had tumours with epithelioid histology. In 10 %, histology was sarcomatoid, and in 17 %, it was mixed. Virtually all patients had received prior chemotherapy. The pembrolizumab doses ranged from 2 mg/kg every 3 weeks to 10 mg/kg every 2 weeks. Most patients received pembrolizumab at a flat dose of 200 mg every 3 weeks.

Outcomes according to PD-L1 expression

Among the 48 patients included in this analysis, one and 11 achieved CR and PR, respectively, which added up to an ORR of 25 %. This was similar to early clinical trial data with PD-(L)-1 inhibitors [11, 12, 14] and compared favourably to current chemotherapy options. With 13 additional patients achieving SD, DCR was 52 %. The median PFS and OS in the entire cohort were 3.6 months and 7.2 months, respectively. Predictors of improved survival with pembrolizumab included good performance status, early line of treatment, and sarcomatoid histology. Survival results obtained in these selected groups resembled those from the KEYNOTE-028 trial and the Chicago cohort [11, 12]. On the other hand, the outcomes in the all-comer population included in this registry were clearly inferior to those observed in the trials.

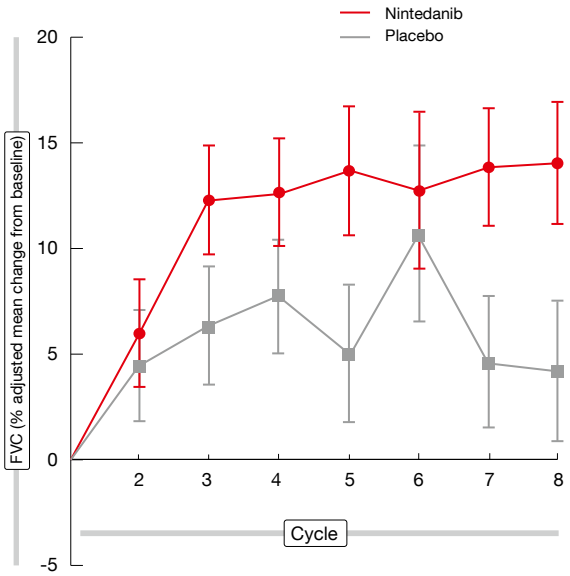

Figure: Adjusted mean percentage in FVC from baseline for patients with epithelioid histology who received either nintedanib or placebo

With regard to PD-L1 expression, results were available for 37 patients. Sixty-seven percent of these were PD-L1–negative by definition (i.e., PD-L1 expression < 5 %), while 22 % and 11 % had PD-L1 expression of 5-49 % and ≥ 50 %, respectively. A significant correlation between histology and PD-L1 expression was found, as PD-L1 negativity prevailed in epithelioid tumours, while high PD-L1 expression correlated with sarcomatoid histology. The PD-L1-positive subgroups showed 4-5 fold higher ORRs compared to the PD-L1–negative cohort. Patients with PD-L1 expression ≥ 50 % achieved a DCR of 100 %. Likewise, PFS and OS improved with increasing PD-L1 expression. Of note, the single patient who achieved complete remission had both sarcomatoid histology and high PD-L1 expression. The authors concluded that these two features might be predictive for improved outcomes with pembrolizumab treatment.

Fifteen treatment-related AEs occurred in 14 patients, with five grade 3/4 AEs, four of which had resolved at the time of data cut-off. Seven patients (15 %) discontinued pembrolizumab treatment due to AEs. An ongoing prospective randomised controlled trial will establish the role of checkpoint inhibition in MPM.

First-line benefit from nintedanib treatment

The oral multikinase inhibitor nintedanib is being investigated in patients with unresected MPM in the randomised, double-blind, placebo-controlled phase II/III LUME-Meso trial. Chemotherapy-naïve patients are treated with either nintedanib 200 mg twice daily plus pemetrexed/cisplatin (n = 44) or placebo plus pemetrexed/cisplatin (n = 43). Patients in the experimental arm without disease progression receive nintedanib maintenance. At the ESMO 2017 Congress, mature OS and forced vital capacity (FVC) results from the phase II part of the trial were reported [15].

A trend towards improvement in OS favouring nintedanib treatment became evident for the whole cohort (18.3 vs. 14.2 months; HR, 0.77; p = 0.3193). The survival benefit conferred by nintedanib treatment was greatest in patients with epithelioid histology (20.6 vs. 15.2 months; HR, 0.70; p = 0.1965). FVC was included as an endpoint because it reflects patient performance and quality of life in MPM. Higher baseline FCV and increases in FVC during treatment correlate with better patient-reported outcomes [16, 17]. Indeed, according to this

analysis, adjusted mean percentage change in FVC from baseline favoured nintedanib over placebo from cycle 2 for all patients and those with epithelioid histology **(Figure)**. The same was true at cycle 8; here, the mean treatment difference was 7.2 % for all patients and 9.9 % for the group with epithelioid histology.

Confirmation of the primary PFS analysis

As for the initial analysis, updated PFS data showed that nintedanib treatment improved PFS compared with placebo (9.4 vs. 5.7 months; HR, 0.54; p = 0.0103). This improvement was greatest in patients with epithelioid histology (9.7 vs. 5.7 months; HR, 0.49; p = 0.0056). Patients in the nintedanib arm developed numerically more objective responses than those in the placebo arm (56.8 % vs. 44.2 %). All of these were partial responses.

The safety profile of nintedanib treatment proved manageable and consistent with previous studies. AEs commonly associated with anti-angiogenic agents were either balanced between treatment arms or reported in fewer patients in the nintedanib arm than in the control arm. In addition, AEs leading to permanent study discontinuation of the last study medication occurred less frequently with nintedanib than with placebo (6.8 % vs. 17.1 %). Nintedanib did not compromise delivery of the backbone chemotherapy. The phase III part of the LUME-Meso study is currently recruiting patients with epithelioid histology. ■

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Characteristics and outcomes for SCLC arising from transformation

A low but significant proportion of *EGFR*-mutant adenocarcinomas transforms to SCLC at the time of acquisition of resistance to EGFR TKI therapy [1]. Moreover, cases of *de novo* SCLC harbouring *EGFR* mutations have been reported [2]. As the clinical characteristics and clinical course of SCLC-transformed *EGFR*-mutant lung cancer are largely unknown, Marcoux et al. retrospectively reviewed the records of 16 patients with *EGFR*-mutant SCLC treated between 2006 and 2017 [3]. According to this analysis, the tumours maintained their founder *EGFR* mutation and were mutually exclusive with T790M. This also applied to cases that had previously been T790M-positive. As with *de novo* SCLC, *EGFR*-mutant SCLC-transformed tumours frequently harboured mutations in *TP53*, *RB1* and *PIK3CA*.

Median PFS of the entire cohort for initial therapy after transformation was 3.3 months. Platinum-etoposide was used as the most common regimen directly after SCLC diagnosis. Responses to platinum-based chemotherapy were frequent, but transient. Among all post-transformation treatment lines considered, the first use of a platinum-based regimen showed a clinical response rate of 72 % and a median PFS of 4.6 months. No responses occurred in five patients who received immune checkpoint inhibitors.

Median OS from initial diagnosis of metastatic lung cancer was 38 months, which is similar to the expected OS in patients who do not undergo SCLC transformation. From SCLC transformation onward, median OS was 8.8 months, which is similar to that observed in patients with *de novo* SCLC. Further investigation is called for to better elucidate optimal diagnostic approaches and treatment strategies for this group of patients. ■

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ALK-positive NSCLC: updates on crizotinib and alectinib

PROFILE 1014 was the first study to define the role of the ALK inhibitor crizotinib in the first-line treatment of patients with *ALK*-positive lung cancer. It compared crizotinib 250 mg twice daily (n = 172) with pemetrexed plus cisplatin (n = 171) in patients with *ALK*-positive, locally advanced, recurrent or metastatic non-squamous NSCLC in the first-line setting. The primary efficacy endpoint (i.e., superiority of crizotinib vs. chemotherapy in terms of PFS) was met, with an HR of 0.454 (median PFS, 10.9 vs. 7.0 months for crizotinib and chemotherapy, respectively; $p < 0.0001$) [1]. ORR was significantly higher with crizotinib than with chemotherapy (74 % vs. 45 %; $p < 0.001$). At that time, median OS had not been reached in either group at data cut-off.

Long-term OS advantage in PROFILE 1014

After a median follow-up of approximately 46 months in both arms, Mok et al. presented the updated OS and safety analysis [2]. According to these data, crizotinib gave rise to a 24 % reduction in mortality risk compared to chemotherapy (HR, 0.76), although this difference was not statistically significant ($p = 0.0978$). Median OS had still not been reached for crizotinib, with a lower margin of 45.8 months, which resembled the median OS of 47.5 months obtained for chemotherapy. The four-year OS rates were 56.6 % vs. 49.1 %. This is one of the highest 4-year survival rates for any TKI therapy in patients with stage IV NSCLC to date.

As crossover had been permitted in PROFILE 1014, the proportion of patients randomised into the chemotherapy arm who received subsequent TKI therapy with crizotinib was substantial. Using a rank-preserving structural failure time model adjusted for crossover, it was estimated that the HR for OS would be 0.346 if no crossover had occurred (median OS, 59.8 vs. 19.2 months). With regard to the impact of subsequent therapies, it was shown that patients who received crizotinib followed by another ALK TKI had the longest OS, whereas those randomised to chemotherapy followed by no ALK TKI or other treatment fared worst **(Figure 1)**. No unexpected toxicities were revealed with long-term crizotinib treatment.

ALEX: head-to head comparison

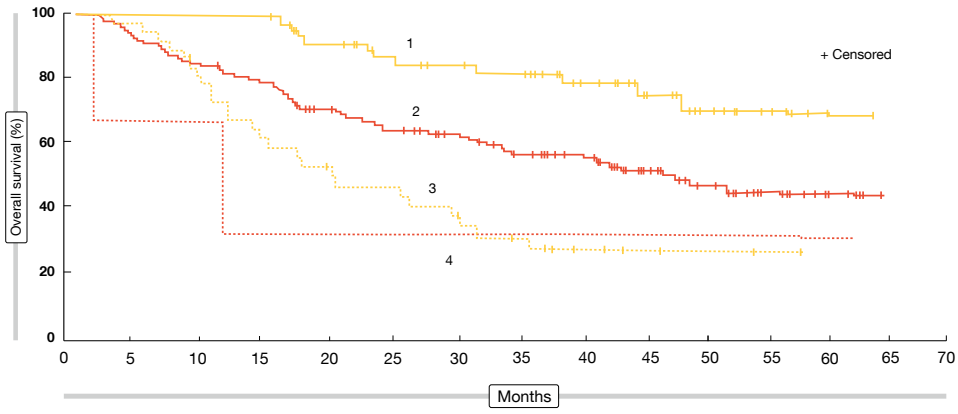
However, as progression is inevitable in patients treated with the first-generation ALK inhibitor crizotinib, further targeted options have become available. The second-generation ALK inhibitor alectinib has shown systemic and CNS efficacy in patients previously treated with crizotinib in two pivotal phase II trials [3, 4]. Based on these studies, alectinib was approved for the treatment of patients with *ALK*-positive NSCLC who have progressed on crizotinib or are intolerant to it.

In the first-line setting, alectinib was compared to crizotinib in the ALEX trial that investigated both the systemic and CNS efficacy of these two drugs in patients with *ALK*-positive, stage IIIB/IV NSCLC. Overall, 303 patients participated in ALEX, with 152 and 151 receiving alectinib 600 mg twice daily and crizotinib 250 mg twice daily, respectively. The primary endpoint of the ALEX study was met: alectinib significantly improved PFS compared to crizotinib (not reached vs. 11.1 months; HR, 0.47; $p < 0.001$) [5].

The CNS is a common site of metastasis and disease progression in *ALK*-positive NSCLC patients. As many as 30 % of patients already have CNS lesions at initial diagnosis [6], and the CNS is the first site of progression in up to 50 % of patients receiving crizotinib [7, 8]. Patients with asymptomatic brain metastases were permitted in the ALEX trial, irrespective of whether treatment for them had been administered or not. All of the patients underwent brain imaging prior to study entry and every 8 weeks thereafter. At the ESMO 2017 Congress, Gadgeel et al. presented the CNS efficacy results from the ALEX trial after a median follow-up of approximately 18 months [9].

Activity across multiple CNS endpoints

Among the total study population, 122 individuals had CNS disease at baseline. Here, 64 were randomised to alectinib and 58 to crizotinib. Approximately 60 % in each arm had not received any treatment for their brain metastases prior to study entry. Compared with crizotinib, alectinib significantly improved PFS both in patients with baseline CNS me-



1: Crizotinib followed by any ALK TKI
2: Chemotherapy followed by any ALK TKI
3: Crizotinib followed by any follow-up therapy other than ALK TKI
4: Chemotherapy followed by any follow-up therapy other than ALK TKI

Figure 1: Impact of various treatment sequences on overall survival

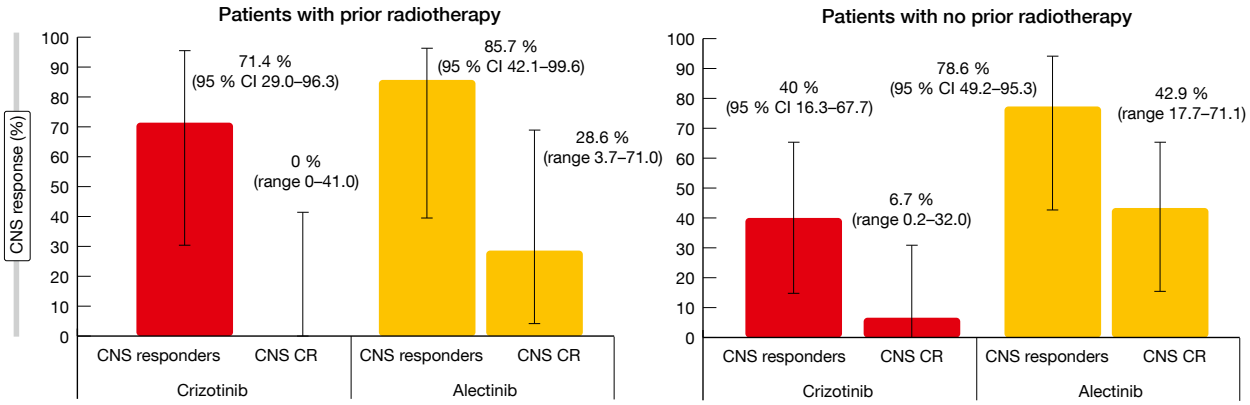


Figure 2: CNS responses in patients with measurable CNS disease in the ALEX trial: patients with (left) and without prior radiation (right)

tastasis (not reached vs. 7.4 months; HR, 0.40; $p < 0.0001$) and those without (not reached vs. 14.8 months; HR, 0.51; $p = 0.0024$). PFS was also assessed by prior radiotherapy in patients with baseline CNS metastasis. Alectinib gave rise to significant PFS prolongation regardless of whether radiotherapy had been administered or not (HRs, 0.34 and 0.44, respectively).

Progression in the CNS at the time of first progression was less frequent with alectinib than with crizotinib in both patients with and without CNS metastases at baseline. This also applied to patients with baseline lesions independent of prior radiotherapy. A key secondary endpoint of the ALEX trial was time to CNS progression. Based on a competing risk analysis, it was shown that alectinib significantly delayed CNS progression both in patients with CNS metastases at baseline (cumulative incidence rates at 12 months, 16.0 % vs. 58.3 % with alectinib and crizotinib, respectively; cause-specific HR, 0.18; $p < 0.0001$) and those without (cumulative incidence rates at 12 months, 4.6 % vs. 31.5 %, respectively; cause-specific HR, 0.14; $p < 0.0001$). This suggests that alectinib has protective effects against the development of CNS progression. Again, alectinib treatment benefited both patients with and without prior radiotherapy concerning the cumulative incidence rate of CNS progression (HRs, 0.11 and 0.22, respectively).

Superiority with respect to intracranial responses

CNS responses according to RECIST were assessed separately in patients with and without prior radiation who had measurable CNS disease at baseline. In those who had received radiotherapy, CNS ORR for alectinib was 85.7 %, and complete remissions in the CNS occurred in 28.6 % **(Figure 2)**. For crizotinib, these rates were 71.4 % and 0 %, respectively. Patients without prior radiation showed CNS overall and complete response rates of 78.6 % and 42.9 %, respectively, for alectinib, and 40.4 % and 6.7 %, respectively, for crizotinib. Duration of response obtained with alectinib also exceeded the corresponding results observed with crizotinib in patients with and without prior radiation.

Similar outcomes resulted for CNS response in patients with both measureable and non-measureable CNS disease at baseline. The group without prior radiotherapy fared best; here, CNS overall response and complete remission rates were 74.4 % and 61.5 %, respectively. For crizotinib, these percentages were 24.3 % and 10.8 %, respectively. Again, alectinib performed better with regard to duration of response in patients with and without prior radiotherapy.

In the ALEX trial, efficacy was also assessed by use of the RANO criteria. The analysis showed that data generated by RECIST and RANO criteria were consistent. According to the RANO criteria, the cumulative incidence rates of CNS progression at 12 months were significantly lower with alectinib than with crizotinib (8.0 % vs. 32.2 %; cause-specific HR, 0.18; $p < 0.0001$). Along with the systemic results, these findings consolidate alectinib as the new standard of care for patients with previously untreated, advanced, *ALK*-positive NSCLC.

ALUR: alectinib versus chemotherapy

Until recently, no studies have directly compared alectinib with standard chemotherapy in patients with *ALK*-positive NSCLC after crizotinib failure. This gap was closed by the randomised phase III ALUR trial. Patients enrolled in this study had already received crizotinib and one line of platinum-based chemotherapy. They were randomised to either alectinib 600 mg twice daily ($n = 72$) or chemotherapy with pemetrexed or docetaxel as per investigator's choice ($n = 35$).

The primary endpoint, which was PFS in the ITT population according to investigator assessment, was met, with an HR of 0.15 [10]. Median PFS was 9.6 vs. 1.4 months ($p < 0.001$). All of the subgroups experienced markedly greater PFS benefit from alectinib treatment than from chemotherapy. Likewise, the analysis according to the independent review committee (IRC) showed a clear advantage for alectinib, with median PFS being 7.1 vs. 1.6 months (HR, 0.32; $p < 0.001$). A similar magnitude of effect was observed for the differences in overall response rates; these were 37.5 % vs. 2.9 % by investigator, and 36.1 % vs. 11.4 % by IRC. Disease control was obtained in 80.6 % vs. 28.6 % according to investigator, and duration of response was 9.3 vs. 2.7 months.

CNS responses confined to the alectinib arm

In ALUR, approximately 70 % of patients in each arm had CNS metastases at the time of study entry. CNS overall re-

sponse rate by IRC in patients with measurable CNS lesions at baseline was defined as a key secondary endpoint of the trial. Alectinib conferred significant benefit with regard to this outcome, as 54.2 % of patients in the experimental arm responded to the treatment **(Table)**. One patient developed CR, and 12 showed PR. In contrast, none of the patients included in the control arm experienced any CNS remissions ($p < 0.001$).

The median time on treatment was more than three times longer with alectinib than with chemotherapy (20 vs. 6 weeks, respectively). Despite this greater exposure to treatment, AEs of all grades occurred less frequently with alectinib compared to chemotherapy (77.1 % vs. 85.3 %). This also applied to grade 3–5 AEs (27.1 % vs. 41.2 %). Furthermore, alectinib therapy showed advantages with respect to AEs leading to treatment discontinuation (5.7 % vs. 8.8 %) and AEs leading to dose reductions (4.3 % vs. 11.8 %).

TABLE
ALUR trial: CNS responses obtained with alectinib and chemotherapy

	Alectinib (n = 24)	Chemotherapy (n = 16)
CNR ORR by IRC, %	54.2	0
p value	< 0.001	
CNS best overall response, n (%)		
Complete response	1 (4.2)	0
Partial response	12 (50.0)	0
Stable disease	6 (25.0)	5 (31.3)
Progressive disease	3 (12.5)	8 (50.0)
Not evaluable	2 (8.3)	3 (18.8)

Overall, the results of the ALUR trial further confirmed the previously proven benefit of alectinib for *ALK*-positive patients with advanced or metastatic NSCLC. ■

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Rare driver mutations: *BRAF*- and *HER2*-mutant NSCLC

First-line dabrafenib plus trametinib

BRAF driver mutations in NSCLC are rare at 2 % [1, 2], but tumours with *BRAF*V600E mutations have histological features suggestive of aggressive biology [3]. When treated with platinum-based chemotherapy, these patients showed less favourable outcomes [3, 4].

The multi-cohort, non-randomised, phase II BRF113928 study investigated a targeted approach using the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib in patients with advanced *BRAF*V600E-mutated NSCLC. This trial contained a dabrafenib monotherapy arm (Cohort A) as well as two combination arms (Cohorts B and C) that received dabrafenib 150 mg twice daily plus trametinib 2 mg daily. Cohort B consisted of pre-treated patients, while Cohort C contained a treatment-naïve population. The primary endpoint for each cohort was investigator-assessed ORR. An independent review committee (IRC) reviewed responses according to RECIST.

The indirect comparison across Cohorts A and B demonstrated higher ORR and longer median PFS with the combined administration of dabrafenib and trametinib than with dabrafenib monotherapy in pre-treated patients. [5, 6]. At the ESMO 2017 Congress, Planchard et al. presented findings obtained in the treatment-naïve Cohort C that comprised 36 patients with stage IV NSCLC [7]. This is the first study of combined BRAF and MEK inhibition as first-line therapy in patients with *BRAF*V600E-mutant metastatic NSCLC.

Fifty-one percent alive at 2 years

The dabrafenib plus trametinib regimen gave rise to substantial anti-tumour activity and durable responses. According to both investigator and IRC assessment, ORR was 64 %. Together with the propor-

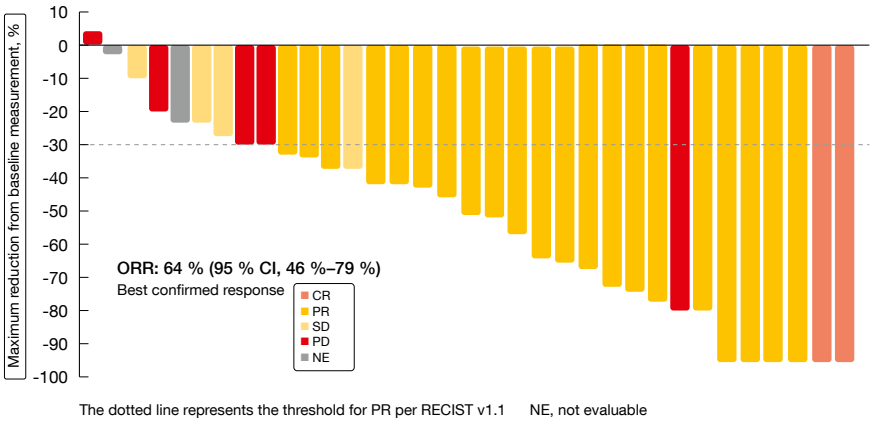

Figure: Investigator-assessed maximum change in target lesions with dabrafenib plus trametinib combination treatment

tion of patients demonstrating SD, this resulted in a DCR of 75 % and 72 % as per investigator and IRC review, respectively. Two patients experienced CR, and 21 achieved PR **(Figure)**. Duration of response was 10.4 and 15.2 months according to investigator and IRC assessment, respectively. Median PFS was 10.9 and 14.6 months, respectively. At 6 months, 72 % and 69 % of patients, respectively, were progression-free. The combination gave rise to a preliminary median OS of 24.6 months. Fifty-one percent of patients were alive at 2 years. ORR, duration of response and PFS resembled those reported for the previously treated cohort receiving combination therapy in BRF113928 [5, 6].

The safety profile proved manageable and was similar to previous experience with the combination. AEs of all grades necessitated treatment discontinuation in 19 % and dose reductions in 31 %. Pyrexia, nausea and diarrhoea constituted the most common AEs. No new safety signals were observed. Based on these results, dabrafenib plus trametinib was recently approved by the EMA and the FDA for use in patients with metastatic NSCLC expressing the *BRAF*V600E mutation, regardless of prior treatment history.

Afatinib in heavily pre-treated patients with *HER2* mutation

Approximately 1–4 % of adenocarcinomas of the lung harbour *HER2* mutations [8], but approved targeted treatments are still lacking for these patients. Afatinib works by irreversibly inhibiting signalling from all ErbB family receptor homodimers and heterodimers, including HER2 [9, 10]. A global named patient use programme initiated in 2010 is providing real-world data on the use of afatinib in global clinical practice for NSCLC patients with no established therapeutic option. Peters et al. reported treatment outcomes for the cohort with *HER2*-mutant NSCLC [11].

The patients treated in the named patient use programme received afatinib 50 mg daily; lower starting doses were allowed at the discretion of the physician. As of April 2017, data were available for 28 patients. More than half of them had been treated with three or more systemic lines. First-generation EGFR TKI monotherapy had been administered in 36 %. Seven patients had already received HER2-directed drugs. All specified *HER2* mutations were identified in exon 20, with the most common mutation type being a 2325/YVMA insertion (n = 8).

The analysis suggested clinically meaningful efficacy of afatinib. Median time to treatment failure (TTF) was 2.9 months; here, patients showing a 2325/YVMA insertion experienced markedly improved TTF (9.9 months) compared to those with other specified *HER2* mutations (1.9 months). In the overall population, 32 % of patients had a TTF of > 1 year. Among 16 patients with available response data, ORR and DCR were 19 % and 69 %, respectively. This is in line with findings from another international, multi-centre study of afatinib in *HER2*-mutant NSCLC [12]. Patients with a 2325/YVMA insertion obtained disease control in 100 %. No unexpected AEs occurred. Based on these results, the evaluation of afatinib in earlier treatment lines in *HER2*-mutant NSCLC patients might be warranted. ■

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