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A GLOBAL CONGRESS DIGEST ON LUNG CANCER

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Preface

Dear Colleagues,

The struggle against the devastating consequences of lung cancer is ongoing at many levels and appears to have reached important milestones, including effective combinations of novel drug classes and the targeting of an increasing number of driver aberrations. Immunotherapy was again a major aspect at this year's annual congress of the European Society for Medical Oncology (ESMO) that took place at Barcelona, Spain, from 27th September to 1st October. Meanwhile, the activity of immune checkpoint inhibitors has been well documented, although of course only a certain percentage of patients will benefit from treatment. Biomarker research has thus become a major focus in the further development of these drugs. Besides PD-L1 expression, other parameters such as tumor mutational burden are being explored, with mixed results.

Immunotherapy improves outcomes when administered together with other therapies such as cytotoxic agents, but also appears to combine well with anti-angiogenic drugs based on synergy at the tumor microenvironment level. These insights might fuel new therapeutic algorithms, particularly in patients without driver mutations. On the other hand, in the setting of *EGFR*-mutant lung cancer, angiogenesis-targeted drugs are also potential combination partners for EGFR tyrosine kinase inhibitors. Studies conducted with combined frontline regimens have revealed convincing findings in this area. More importantly, new evidence has also been generated on the topic of the ideal treatment sequence in patients with *EGFR*-positive disease. The use of third-generation EGFR TKI emerges as the preferred therapeutic strategy in the first-line setting for *EGFR*-positive patients.

Another important field of research is the identification and targeting of rare fusions such as those of the *ALK*, *ROS1*, *NTRK*, *RET* and *NRG1* genes. Despite low prevalence rates, this is worth the effort as it can enable very successful treatment in a setting where other options might not elicit meaningful responses. Novel and known agents are being assessed for their activity in rare aberrations.

Finally, essential steps have been taken by eventually improving survival in patients with small-cell histology.

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Immunotherapy has established new horizons in small-cell tumors, with recent analyses showing that these benefits are independent of the biomarker status.

In their entirety, these new insights will hopefully contribute to improving treatment and adding precious time and quality of life to our patients' lives.

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Checkpoint inhibition in non-small-cell lung cancer: expanding the range of options

IMpower110: interim OS findings

The randomized phase III IMpower110 trial is evaluating the PD-L1 inhibitor atezolizumab as first-line treatment in patients with stage IV, PD-L1–positive non-small-cell lung cancer (NSCLC) independent of tumor histology. Patients in the experimental arm are treated with atezolizumab until disease progression, while the platinum-based chemotherapy regimens administered in the control arm for 4 to 6 cycles depend on histology. Patients were stratified according to their PD-L1 expression on tumor-infiltrating immune cells (IC1/2/3) and tumor cells (TC1/2/3). Approximately one third showed the highest PD-L1 expression (TC3 or IC3).

At the ESMO 2019 Congress, Spigel et al. reported the interim results for overall survival (OS) in the wildtype population, i.e., the patients without *EGFR* and/or *ALK* aberrations, which was defined as the primary endpoint [1]. OS assessments followed hierarchical testing, with the analysis of the TC3 or IC3 subgroup preceding evaluation of the TC2/3 or IC2/3 group, which again preceded the assessment of the TC1/2/3 or IC1/2/3 population (i.e., the total population).

Benefits across histologies

Patients in the TC3 or IC3 subgroup (n = 205) derived clinically meaningful benefits from atezolizumab compared to chemotherapy. Median OS was 20.2 vs. 13.1 months (HR, 0.59; p = 0.0106; **Figure 1**), and survival rates at 12 months amounted to 64.9 % vs. 50.6 %. Objective responses occurred in 38.3 %

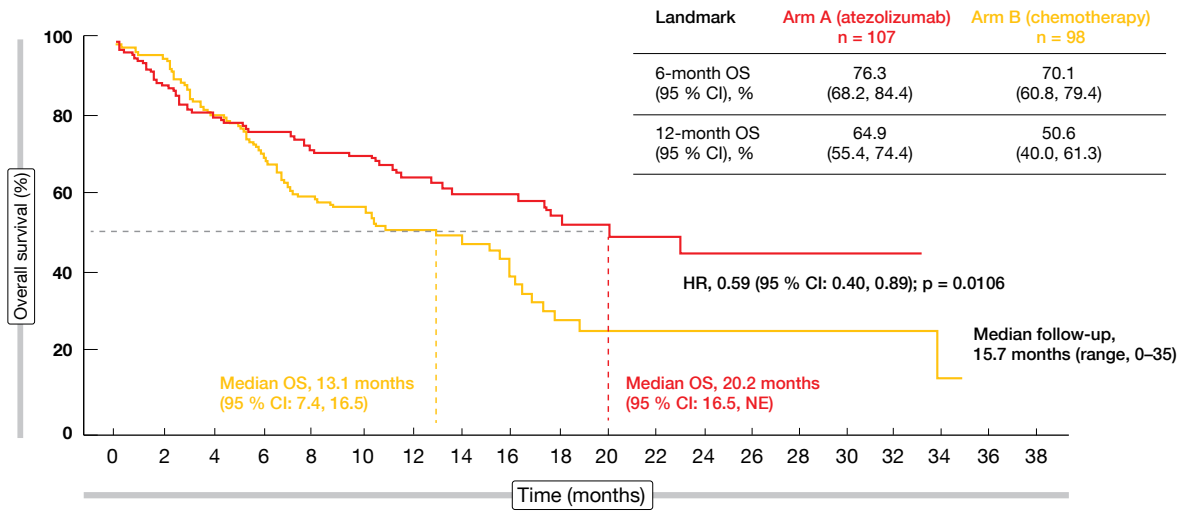

Figure 1: Overall survival benefit with atezolizumab compared to chemotherapy in the TC3 or IC3 subgroup of the IMpower110 trial

and 28.6 %, respectively. While the median duration of response had not yet been reached in the experimental arm, it was 6.7 months in the control arm. In the TC2/3 or IC2/3 subgroup (n = 328), the pre-specified OS boundary had not been crossed at the time of the analysis, although the results favored atezolizumab (18.2 vs. 14.9 months). Therefore, the TC1/2/3 or IC1/2/3 population (n = 554) was not formally tested.

Likewise, progression-free survival (PFS) will only be formally assessed once the primary endpoint is positive for all three populations. The current analysis showed median PFS of 8.1 vs. 5.0 months in the TC3 or IC3 subgroup (HR, 0.63) as well as superiority of the atezolizumab treatment for PFS in the TC2/3 or IC2/3 subgroup and the total population. Response rates did not differ across treatment arms in the TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 populations. Additional biomarker analyses will be presented at a future congress. The authors noted that atezolizumab represents a promising first-line treatment option in NSCLC patients with high PD-L1 expression.

Final analysis of B-F1RST

The phase II B-F1RST trial was the first prospective evaluation of blood tumor mutational burden (bTMB) as a predictive biomarker for patients with metastatic NSCLC receiving first-line atezolizumab monotherapy. According to the primary analysis presented in 2018 [2], the pre-specified bTMB cutoff score of 16 correlated with numerical clinical benefits. Socinski et al. presented the final analysis of the B-F1RST trial after a follow-up period of ≥ 18 months at ESMO 2019 [3].

These data showed that single-agent atezolizumab provides outcome improvements in a real-world, unselected population. Objective response rates (ORRs) in the intent-to-treat (n = 152) and biomarker-evaluable (n = 119) populations were 17.1 % and 12.6 %, respectively. Median duration of response in the ITT population was 16.3 months. Median OS will continue to be followed. Also, the analysis corroborated the predictive potential of the bTMB cutoff score of 16. This applied to PFS (5.0 vs. 3.5 months for bTMB-high vs. bTMB-low cohorts; HR, 0.80; p = 0.35), ORR (35.7 % vs. 5.5 %; p < 0.0001) and OS (23.9 vs. 13.4 months; HR, 0.66; p = 0.18). Exploratory analyses demonstrated improved clinical benefit with increasing bTMB cutoff.

The scientists concluded that a blood-based assay can measure TMB in the absence of adequate tissue and predict numerical PFS and OS benefits if a chemotherapy-free first-line option is wished for. Another exploratory endpoint of the trial was serum C-reactive protein (CRP), which was measured at baseline and on day 1 of cycle 3 while on atezolizumab treatment. Decreases in CRP during this time were shown to be associated with improved OS.

TMB as a biomarker: pembrolizumab monotherapy …

Based on the observation that a relationship between high TMB levels and improved OS has not been unequivocally established for treatment with the PD-1 inhibitor pembrolizumab, Herbst et al. assessed the predictive power of tissue (tTMB) according to whole exome sequencing in the open-label KEYNOTE-010 and KEYNOTE-042 trials [4]. These had tested pembrolizumab monotherapy against chemotherapy in the second-line and first-line settings, respectively, in patients with PD-L1–expressing (TPS ≥ 1 %) advanced NSCLC [5, 6].

In KEYNOTE-010, the tTMB-evaluable population comprised 253 individuals. According to the exploratory analysis, tTMB was associated with OS, PFS and ORR for pembrolizumab as a continuous variable, but not with chemotherapy. The phase III KEYNOTE-042 trial included 793 tTMB-evaluable patients. As for KEYNOTE-010, this analysis demonstrated an association of tTMB with outcomes for pembrolizumab as a continuous variable, but not with response to chemotherapy in general. In both trials, the samples of tTMB-evaluable patients were deemed representative due to comparability of baseline characteristics and outcomes across these cohorts and the overall populations.

For both KEYNOTE-010 and -042, the tTMB cutpoint of ≥ 175 mutations per exome showed clinical utility. This cutpoint provided a distinct separation for the results obtained with pembrolizumab *versus* chemotherapy with respect to OS, PFS, and ORR **(Figure 2)**. Neither analysis revealed a relationship between tTMB and PD-L1 expression

for pembrolizumab or chemotherapy. In their conclusion, the authors noted that tTMB may provide additional information regarding the clinical benefit of pembrolizumab monotherapy in patients with PD-L1–positive advanced NSCLC in the first-line and previously treated settings. This might represent another step in the process of personalization of immunotherapy.

… and pembrolizumab-chemotherapy combination

Different results were reported for another exploratory analysis that related to the association of tTMB with the outcomes obtained in patients who received pembrolizumab together with chemotherapy. Data were obtained from the KEYNOTE-21 cohorts C and G, as well as the KEYNOTE-189 and -407 trials [7]. All of these had been conducted in the first-line setting and had tested pembrolizumab plus platinum-based chemotherapy. Cohort C of the KEYNOTE-21 study assessed two different pembrolizumab doses [8], while Cohort G [9, 10], KEYNOTE-189 [11] and KEYNOTE-407 [12] contained chemotherapy-only control arms. Patients included in KEYNOTE-407 had squamous histology, whereas all of the other trial participants had been diagnosed with non-squamous NSCLC. Whole exome sequencing was used to quantify tTMB. Overall, 675 tTMB-evaluable patients representative of the total populations of their respective trials provided data for this analysis.

None of the studies showed a significant association between tTMB and the efficacy of pembrolizumab plus chemotherapy or platinum-based chemotherapy alone. OS, PFS, and ORR benefits occurred with pembrolizumab plus histology-specific chemotherapy in both tTMB-high and tTMB-low subgroups. Again, there was no relationship between tTMB and PD-L1 expression. These data suggest that tTMB has limited clinical utility in the setting of first-line pembrolizumab plus platinum-based chemotherapy for both metastatic squamous and non-squamous NSCLC.

Durable improvements in KEYNOTE-407

As noted above, the phase III KEYNOTE-407 trial investigated pembrolizumab plus chemotherapy compared to chemotherapy alone in patients with advanced, previously untreated metastatic squamous NSCLC. The addition of the PD-1 inhibitor has been shown to induce significant OS and PFS benefits [12]. According to the protocol-specified final analysis reported at ESMO 2019, pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel continued to demonstrate improved outcomes compared to chemotherapy [13]. After a median follow-up of 14.3 months, median OS was 17.1 vs. 11.6 months (HR, 0.71), and median PFS amounted to 8.0 vs. 5.1 months (HR, 0.57). Responses differed by 24.1 % (62.6 % vs. 38.4 %), and they lasted much longer in the combination arm (8.8 vs. 4.9 months). The results were consistent across PD-L1 expression groups, including in patients with PD-L1 TPS < 1 %.

Moreover, the authors estimated PFS2, which is defined as the time from randomization to objective tumor progression on next-line treatment or death from any cause, whichever occurs first. Here, the analysis demonstrated substantial improvement for patients treated with pembrolizumab (13.8 vs. 9.1 months; HR, 0.59). Overall, the KEYNOTE-407 findings continue to support pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel as a standard-of-care first-line regimen in patients with metastatic squamous NSCLC, regardless of PD-L1 expression status.

CheckMate 227: a potential first-line option

The first-line combination of the PD-1 inhibitor nivolumab and the anti-CTLA-4 antibody ipilimumab was investigated by the randomized, open-label, phase III CheckMate 227 study conducted in patients with advanced NSCLC who showed PD-L1 expression of ≥ 1 % (Part 1a) or < 1 % (Part 1b). In Part 1a, patients were randomized to either nivolumab plus low-dose ipilimumab, chemotherapy, or single-agent nivolumab. Part 1b compared nivolumab plus low-dose ipilimumab with chemotherapy and with nivolumab plus chemotherapy. CheckMate 227 had two independent co-primary endpoints that included PFS in the TMB-high (i. e., ≥ 10 mut/Mb) population on one hand and OS in the PD-L1 ≥ 1 % population on the other; both comparisons related to nivolumab plus ipilimumab *versus* chemotherapy.

Peters et al. presented the final results for the OS endpoint at the conference [14]. Irrespective of PD-L1 expression, 583 patients had been randomized to the combination and to chemotherapy each. In Part 1a, 396 individuals had received nivolumab monotherapy.

Successful dual approach

CheckMate 227 met its primary endpoint of OS in patients with PD-L1 ≥ 1 % and is the first phase III study to demonstrate that PD-1 plus CTLA-4 inhibition is effective in NSCLC. Median OS was 17.1 vs. 14.9 months with nivolumab plus ipilimumab and chemotherapy, respectively (HR, 0.79; p = 0.007; **Table**). At 24 months, 40 % vs. 33 % of patients were alive. The risk of progression and death decreased by 18 % (HR, 0.82), with 22 % vs. 7 % remaining progression-free at 24 months. Nivolumab plus ipilimumab gave rise to deep and durable responses. ORRs amounted to 35.9 % vs. 30.0 %, and responses lasted

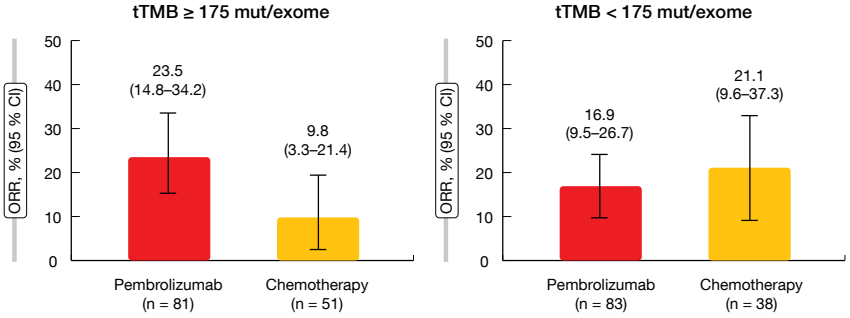

Figure 2: Clinical utility of the tissue tumor mutation burden cutpoint of 175 mutations per exome for objective response rates in KEYNOTE-010

longer in the combination arm (23.2 vs. 6.2 months).

Clinically meaningful survival improvement was observed with the combination regimen compared to chemotherapy regardless of PD-L1 expression, as both patients with scores ≥ 50 % and < 1 % benefited **(Table)**. In all randomized patients, median OS was 17.1 vs. 13.9 months for nivolumab plus ipilimumab and chemotherapy, respectively (HR, 0.73). No consistent correlation existed between survival outcomes and PD-L1 expression or TMB alone or in combination. The CheckMate 227 trial revealed no new safety signals for nivolumab plus low-dose ipilimumab. In their conclusion, the authors pointed out that this dual immunotherapeutic regimen represents a potential new first-line option for patients with advanced NSCLC. ■

TABLE
CheckMate 227: outcomes for nivolumab plus ipilimumab *versus* chemotherapy according to PD-L1 expression

	Nivolumab plus ipilimumab	Chemotherapy	HR
PD-L1 expression ≥ 1 %			
Overall survival (months)	17.1	14.9	0.79
Progression-free survival (months)	5.1	5.6	0.82
Objective response rate (%)	35.9	30.0	
Duration of response (months)	23.2	6.2	
PD-L1 expression ≥ 50 %			
Overall survival (months)	21.2	14.0	0.70
Progression-free survival (months)	6.7	5.6	0.62
Objective response rate (%)	44.4	35.4	
Duration of response (months)	31.8	5.8	
PD-L1 expression < 1 %			
Overall survival (months)	17.2	12.2	0.62
Objective response rate (%)	27.3	22.0	
Duration of response (months)	18.0	4.8	

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EGFR-positive tumors: the issue of optimal therapy across several lines

FLAURA: OS with first-line osimertinib

In patients with advanced, *EGFR*-positive NSCLC, EGFR tyrosine kinase inhibitors (TKIs) represent the frontline treatment standard. Three generations of TKIs are widely available, but the ideal sequence is currently unknown. The phase III, double-blind, randomized FLAURA trial compared the third-generation EGFR TKI osimertinib with the first-generation agents gefitinib and erlotinib in the frontline setting. At the time of the primary analysis, which

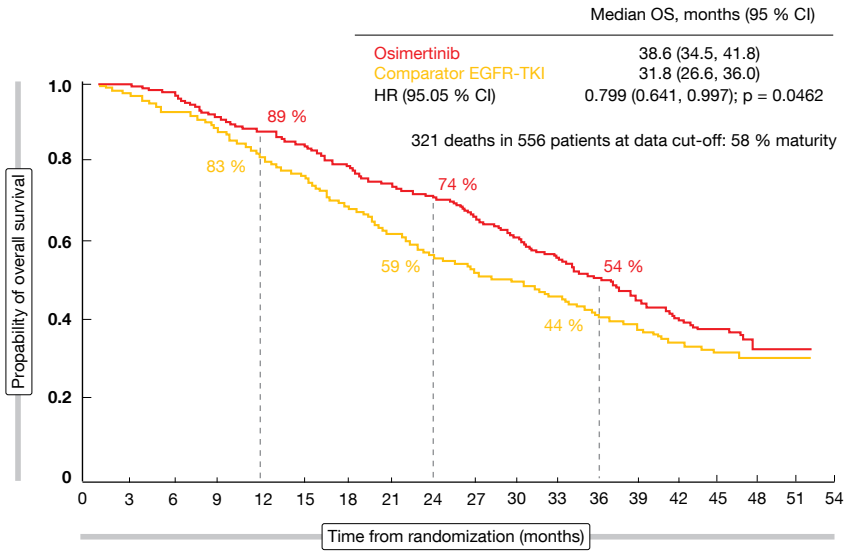


Figure 1: Final overall survival results for osimertinib vs. gefitinib or erlotinib in the FLAURA trial

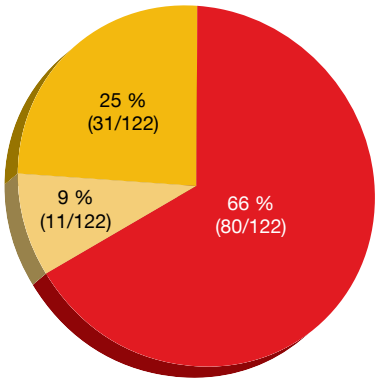
had shown a significant PFS benefit for osimertinib (18.9 vs. 10.2 months; HR, 0.46; p < 0.001), survival outcomes had not been mature yet [1]. Ramalingam et al. presented the final results for OS, which was defined as a key secondary endpoint of the study, at ESMO 2019 [2].

FLAURA demonstrated a statistically significant and clinically meaningful OS improvement with osimertinib compared to gefitinib or erlotinib (38.6 vs. 31.8 months; HR, 0.799; p = 0.0462; **Figure 1**). At 24 months, 74 % vs. 59 % of patients were alive; at 36 months, this applied to 54 % vs. 44 %. As OS was a secondary endpoint, the trial was not powered to assess OS effects in each subgroup. However, all patients derived OS benefit from the third-generation TKI treatment compared to the control arm, although the magnitude of benefit was greater in the non-Asian subgroup than in the Asian cohort. For Asian patients, the Kaplan Meier curves indicate a survival advantage throughout the first three years of the study. At 36 months, a high degree of censoring and a smaller number of events render interpretation difficult.

Subsequent treatments

The duration of time to first subsequent therapy or death observed in the osimertinib arm was almost double that obtained with the comparator agents (25.5 vs. 13.7 months; HR, 0.478; p < 0.0001). At 36 months, 28 % vs. 9 % of patients remained on study treatment. Thirty percent in both trial arms were not able to receive any subsequent therapy, and the majority of these died after the onset of disease progression. In the osimertinib arm, 47 % of patients who experienced progression went on second-line anticancer treatment, which mainly consisted of cytotoxic chemotherapy (68 %). Sixty-five percent of those in the comparator arm received second-line treatment, with osimertinib being the most commonly prescribed agent (47 %). Chemotherapy was administered in 22 % in this group.

Despite prolonged exposure in the experimental arm of FLAURA that exceeded exposure in the comparator arm (20.7 vs. 11.5 months), osimertinib showed a favorable toxicity profile that was consistent with known findings. A comparatively smaller proportion of patients on third-generation TKI therapy developed possibly treatment-related grade ≥ 3 adverse events (18 % vs. 29 %). The authors noted that the final OS analysis of FLAURA reinforces osimertinib as the standard of care for frontline treatment of patients with *EGFR*-mutant advanced NSCLC. Osimertinib is the first EGFR TKI monotherapy to show a statistically significant OS benefit compared to another EGFR TKI.



Red: ctDNA progression at the same time or earlier than RECIST progression
Light yellow: ctDNA progression after RECIST progression
Dark yellow: No ctDNA progression

Figure 2: Timing of ctDNA progression in relation to the onset of RECIST progression with first-line osimertinib

Liquid monitoring of early signs of progression

An exploratory analysis of the FLAURA study investigated serial circulating tumor DNA (ctDNA) for the early molecular detection of progressive disease and resistance mechanisms [3]. Among 556 patients randomized in FLAURA, 122 were eligible for ctDNA analyses (42 and 80 in the osimertinib and comparator arms, respectively). C797S and T790M were the only resistance mutations tested for.

ctDNA progression preceded or co-occurred with disease progression according to RECIST in 66 % of patients across both treatment arms **(Figure 2)**. Median ctDNA progression lead times were similar for osimertinib and comparator EGFR TKI therapy (3.0 vs. 2.6 months). Resistance mutations emerged in 47 % of 122 patients with ctDNA progression. Testing identified C797S mutations in 8 % of the osimertinib-treated population after a median of 16.7 months, while T790M was found in the comparator arm in 74 % after 8.4 months. Overall, the median time from detection of the resistance mutation to RECIST disease progression was 1.4 months. According to this analysis, longitudinal ctDNA monitoring has the potential to detect early signs of progression and acquired resistance mutations ahead of disease progression. Further analyses using next-generation sequencing are ongoing.

Insights into osimertinib resistance

Resistance mechanisms to osimertinib treatment were identified by another analysis based on data from 31 patients included in the prospective MATCH-R

study [4]. This study assessed the evolution of clonal architecture of tumors from patients treated with targeted drugs. Tissue and plasma biopsies were performed at the time of progression on osimertinib and, optionally, before. All molecular oncogenic alterations were reviewed and classified as definitive/potential resistance mechanisms or concomitant genetic alterations.

This analysis suggested that resistance mechanisms to osimertinib are heterogeneous and more complex than expected. More than one alteration was detected in 45 % of patients; 19 % had one resistance mechanism, 29 % two, and 16 % three. *TP53* mutation was the most frequent co-occurring aberration (71 %). Co-occurring genetic alterations correlated significantly with the number of resistance mechanisms (p = 0.002). On-target mechanisms (e. g., *EGFR* aberrations, *RET* and *MET* rearrangements) were identified in 39 %, whereas off-target aberrations (e. g., *NTRK1* rearrangements, *KIF5B-RET* fusions, *MET* amplifications, *KRAS* and *NRAS* mutations) were present in 26 %. In 35 %, the resistance mechanisms remained unknown.

T790M loss co-occurred more frequently with unknown mechanisms of resistance and was associated with a more aggressive progression pattern resulting in shorter time to treatment discontinuation compared to patients who maintained T790M (13 vs. 22 months; HR, 2.16; p = 0.046). Overall, the analysis revealed a considerable number of confirmed fusions (16 %), with some of them being potentially targetable. The scientists stated that combined treatment strategies might be needed to improve clinical outcomes.

GioTag: afatinib followed by osimertinib

Progression on EGFR TKI therapy is inevitable, which raises the question of subsequent treatment. Several considerations provide a rationale for the sequential use of afatinib and osimertinib. The gatekeeper *EGFR* T790M mutation represents the predominant mechanism of acquired resistance to first- and second-generation EGFR TKIs. T790M incidence rates for the second-generation agent afatinib have been estimated at 50 % to 70 % [5-8] and even 75 % for patients with deletion-19–positive disease [9]. Therefore, most patients progressing on afatinib will be eligible for second-line osimertinib, which has shown pronounced activity against T790M-positive disease in the AURA3 trial [10]. In contrast, no single prevailing resistance mechanism has been identified after progression on osimertinib [11, 12]. Here, targeted options are lacking, and chemotherapy will follow in the majority of cases.

TABLE 1
Overall survival and time to treatment failure with afatinib followed by osimertinib in the GioTag trial

	Total population (n = 203)	Deletion 19 (n = 149)	L858R mutation (n = 53)
Overall survival, months	41.3	45.7	35.2
2-year survival rate, %	80	82	
Time to treatment failure, months	28.1	30.6	21.1

Based on these observations, the global observational GioTag study assessed clinical outcomes in patients who were switched to osimertinib after developing the T790M mutation on first-line treatment with afatinib. Sites in ten countries across Europe, Asia and North America participated in the study. A considerable proportion of patients enrolled in GioTag would have been excluded from clinical trials due to decreased ECOG performance status (PS) or cerebral lesions. ECOG PS ≥ 2 and stable brain metastases were present in 15 % and 10 %, respectively.

The interim updated analysis reported at ESMO 2019 by Hochmair et al. revealed a median OS of 41.3 months in the total population of 203 patients **(Table)** [13]. Eighty percent were alive at 24 months. In the group with deletion-19–positive tumors, median OS was 45.7 months, and the 2-year survival rate amounted to 82 %. Median time to treatment failure (TTF) was 28.1 and 30.6 months for the whole group and patients with deletion 19, respectively.

For osimertinib treatment alone, TTF was 15.6 months, which indicates that substantial clinical benefit can be achieved with this agent in the second-line setting following afatinib. In the FLAURA trial, median exposure to first-line osimertinib had been 16.2 months [1]. The authors concluded that sequential afatinib followed by osimertinib is a feasible strategy for patients with *EGFR*-mutant NSCLC. Prospective data are required to evaluate OS of patients treated with different EGFR TKIs and sequential regimens.

German and French sequencing data

Further real-world analyses add to the evidence supporting sequential treatment. In the prospective, non-interventional real-world GIDEON study that was conducted at 49 centers across Germany, 151 patients with advanced, *EGFR*-positive NSCLC received front-line afatinib. Data obtained from 29 patients who were treated with afatinib followed by osimertinib in any later line suggest that this regimen might provide optimal outcomes [14]. Two years after the initiation of afatinib treatment, 89.3 % of patients were alive. Median OS data had not reached maturity at the time of the analysis. In keeping with published data [15], the number of patients in the GIDEON study who received later-line osimertinib was higher in the deletion 19 subgroup than in the other *EGFR* mutation subgroups.

Also, the TKIseq study that was based on the French nationwide claims and hospitalization database identified the sequence as a feasible strategy for patients with acquired T790M mutations [16]. Girard et al. assessed time on treatment, OS, healthcare resources and costs in patients treated with first- or second-generation EGFR TKIs followed by osimertinib in a real-world setting. A total of 576 patients with advanced, *EGFR*-mutant NSCLC were included in the analysis. Median time on treatment (i.e., duration from the first delivery claim of first- or second-generation TKIs until the discontinuation of osimertinib or death) was 34 months. At 24 months, 64.8 % of patients still received

EGFR TKI therapy; at 36 months, this applied to 48.2 %. First-line treatment was administered for a median of 13.6 months, and the median time on osimertinib was 11.9 months. Overall survival for the sequential strategy amounted to 37.1 months. At 36 months, 51.6 % of patients were alive. For the overall population, the mean total direct medical costs per patient per year added up to 62,806 €. The cost of TKI treatment represented 77 % of the overall amount.

First-line afatinib in the real-world setting

Real-world evidence underscores the activity of afatinib as a frontline agent. The global, prospective, single-arm, phase IIIb 1200.55 study evaluated the efficacy and safety of first-line afatinib in a patient population with *EGFR*-mutated NSCLC [17]. At the time of the analysis, a total of 479 patients had been treated. Most of these had ECOG PS 1 (57 %), and brain metastases were present in 17 %. Thus, the study population contained a certain percentage of patients who would not have been eligible for clinical trials.

Nevertheless, the interim efficacy and safety results were consistent with findings from the pivotal LUX-Lung 3, 6, and 7 trials [18-20]. Median time to symptomatic progression (TTSP) and PFS were 14.9 and 13.4 months, respectively. Clinical benefits occurred across a range of subgroups including patients with ECOG PS 2, asymptomatic brain metastases, uncommon *EGFR* mutations, and ≥ 1 previous line of therapy. Prolonged efficacy was observed in those with deletion 19 (19.3 and 15.9 months for TTSP and PFS, respectively) and ECOG PS 0/1 (15.8 and 13.8, respectively). Forty-six percent responded to treatment, and 86 % achieved disease control. Diarrhea and rash were the most common adverse events; both were generally manageable with dose reductions and led to few treatment discontinuations (3 % and 1 % for diarrhea and rash, respectively).

A combined analysis pooled the outcomes obtained in the 1200.55 study and another large, prospective phase IIIb trial that evaluated afatinib in EGFR-TKI–naïve patients under real-world conditions [21]. Overall, 1,020 patients were included, 68.8 % of whom had ECOG PS 1. Brain metastases and uncommon *EGFR* mutations were present at baseline in 18 % each. Thirty-one percent of patients had received one or more previous treatment lines.

This pooled analysis revealed encouraging efficacy as well as a predictable and manageable safety profile consistent with findings from the LUX-Lung trials [18-20]. Median TTSP and PFS in the overall population were 14.6 and 12.9 months, respectively. Objective responses occurred in 52.7 % and lasted for 12.9 months. Almost 90 % of patients achieved disease control, which was maintained for 13.9 months. Dose reductions from 40 mg/d to 30 mg/d were performed in 40.5 %; in another 12.1 %, doses were further reduced to 20 mg/d.

Obstacles to the implementation of sequencing

As the implementation of EGFR TKI sequencing in clinical practice is often difficult, a retrospective analysis conducted in Germany evaluated the clinical course of patients with *EGFR*-mutant NSCLC who were treated with first-/second-generation TKIs and had their last follow-up after osimertinib approval [22]. The aim of the analysis was to better understand patient disposition and limitations in the real-world setting.

Initial TKI treatment consisted mainly of afatinib (49 %), followed by erlotinib (36 %) and gefitinib (15 %). Within the group of 186 patients with first-/second-generation TKI failure, T790M testing was performed in 153 individuals (85 %), and in 84 (55 %), the T790M mutation was identified **(Figure 3)**. Six patients died without documented progression but had treatment discontinuations or switches mainly

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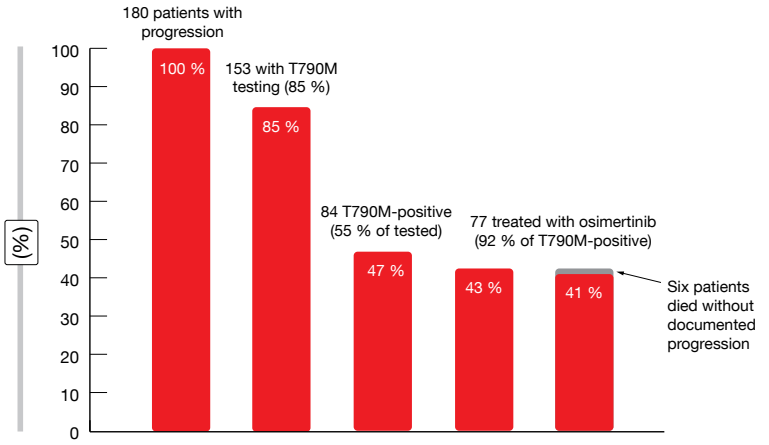

Figure 3: T790M testing and osimertinib treatment rate in 186 patients with failure on first- and second-generation EGFR TKI therapy

due to adverse events. Eventually, 41 % of patients initially treated with first- or second-generation EGFR TKIs received osimertinib. Median OS from the start of the treatment was 35 months for the group with frontline TKI failure. Patients who were prescribed osimertinib thereafter fared significantly better than those with other next-line agents or no subsequent therapy (median OS, 52 vs. 25 months; $p < 0.001$).

The authors noted that the main obstacles to sequential EGFR TKI treatment were lack of T790M testing and T790M-negative progression. Approximately 25 % of patients did not receive next-line treatment after failure of the first-line EGFR TKI; this percentage was much higher in the group not undergoing T790M testing (77 %) than among T790M-tested patients (14 %). More than 90 % of T790M-positive patients eventually received osimertinib. ■

Frontline combinations of EGFR- and angiogenesis-targeted agents

In patients with untreated *EGFR*-mutant tumors, it has been shown that the addition of the anti-VEGF antibody bevacizumab to first-generation EGFR TKIs induces PFS benefits with an acceptable toxicity profile [1, 2]. The open-label, randomized, multicenter, phase III ARTEMIS (CTONG 1509) study is the first phase III trial to test bevacizumab plus erlotinib in Chinese NSCLC patients [3]. At 14 sites in China, a total of 311 patients with *EGFR*-mutated (i. e., exon 19 deletion or exon 21 L858R mutation), advanced NSCLC received either bevacizumab plus erlotinib (n = 157) or erlotinib (n = 154) until progression. PFS according to independent review committee (IRC) constituted the primary endpoint.

PFS difference of up to 10 months

The addition of bevacizumab indeed induced statistically significant and clinically relevant PFS improvement (18.0 vs. 11.3 months; HR, 0.55; $p < 0.001$). Subgroup analyses showed that patients with L858R mutations and those with brain metastases at baseline appeared to derive particular PFS benefit from the combined approach. For the group with L858R mutations that made up approximately half of the total cohort, median PFS was 19.5 vs. 9.7 months by IRC (HR, 0.51; **Figure**), thus exceeding the PFS findings observed for deletion 19 (17.9 vs. 12.5 months; HR, 0.62). Response rates were generally high and did not differ across treatment arms. ORRs were 86.3 % vs. 84.7 % according to IRC, and disease control occurred in 95.9 % vs. 96.5 %. However, duration of response was longer with bevacizumab plus erlotinib than with erlotinib alone (16.6 vs. 11.1 months according to IRC; HR, 0.59). Adverse events related to the combination therapy proved tolerable

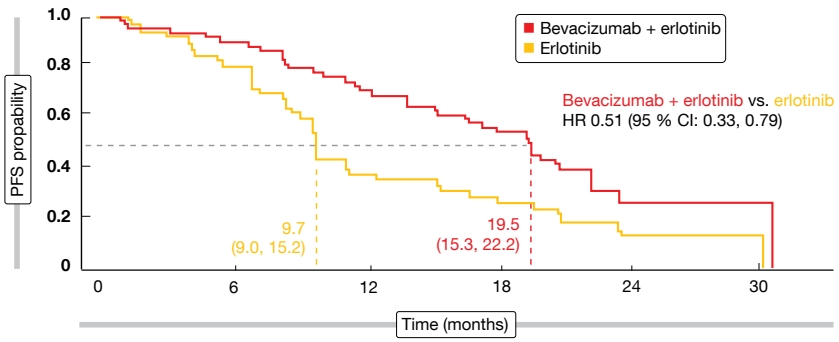

Figure: Progression-free survival benefit with bevacizumab plus erlotinib observed in patients harboring exon 21 L858R mutations

and manageable. No new safety signals were detected.

The study included a resistance biomarker analysis that involved testing of tissue samples using next-generation sequencing and transcriptome sequencing. At the time of progression, the *EGFR* T790M resistance mutation was identified less frequently in the combination arm than with erlotinib (33 % vs. 42 %). Also, patients in the experimental arm showed a smaller proportion of new mutations and amplifications, which implies different resistance mechanisms. The authors concluded that bevacizumab plus erlotinib is expected to become the new first-line standard for the treatment of advanced, *EGFR*-mutant NSCLC.

Resistance mechanisms in RELAY

Another antiangiogenic agent investigated as a combination partner of EGFR-targeted agents is the anti-VEGF-2 antibody ramucirumab. In the global, phase III RELAY trial, patients with *EGFR*-mutation–positive NSCLC were randomized to either ramucirumab combined with erlotinib or placebo plus erlotinib. Compared to erlotinib monotherapy, the combination improved median PFS to a significant extent (19.4 vs. 12.4 months; HR, 0.591; $p < 0.0001$) [4]. An exploratory Japanese substudy of RELAY focused on the occurrence and clinical effect of the T790M mutation as an acquired resistance mechanism [5]. *EGFR* mutations were determined using ctDNA from plasma samples collected before treatment, during treatment, and after disease progression. The biomarker-evaluable population included 65 individuals.

According to this analysis, post-progression T790M mutation rates did not differ between treatment groups despite the PFS advantage conferred by the combination. T790M rates, when analyzed according to the number of treatment cycles before progression, were comparatively lower with ramucirumab plus erlotinib than with erlotinib, although not significantly so. Thus, the combination might delay the occurrence of resistance due to T790M mutations. PFS was not markedly affected by the presence or absence of the T790M mutation in either treatment group. Post-progression T790M rates detected by droplet digital polymerase chain reaction corresponded to those in the overall intent-to-treat population detected by next-generation sequencing, suggesting the potential for effective EGFR-directed therapy after progression on ramucirumab plus erlotinib.

Bevacizumab plus afatinib

Based on the hypothesis that the combination of bevacizumab with the second-generation EGFR TKI afatinib might improve efficacy, the phase I Okayama Lung Cancer Study Group Trial 1404 assessed afatinib plus bevacizumab as frontline treatment in 19 patients with advanced *EGFR*-positive NSCLC. Evidence of disease control including responses in 13 out of 16 evaluable patients has been reported in 2018 [6]. Ninomiya et al. presented the secondary endpoints, which included response rate, PFS, OS and toxicity, at ESMO 2019 [7].

After a median follow-up of 27.4 months, PFS was 24.2, months, and median OS had not been reached yet. The PFS findings did not differ according to the type of *EGFR* mutation (24.2 and 23.8 months for deletion 19 and L858R mutation, respectively). However, patients with ECOG PS 0 showed significantly longer PFS than those with PS 1 (not reached vs. 13.4 months; $p = 0.0192$). ORR amounted to 81.3 % in the total population, with complete responses occurring in 6.3 %.

At two years, seven patients were still on treatment, while five had discontinued due to disease progression, four due to toxicity, and three based on their preference. Rebiopsies showed the presence of T790M mutation at the time of progression in two cases, and osimertinib was prescribed. Among adverse events, acneiform rash, diarrhea, paronychia, proteinuria and hypertension occurred most commonly. No grade ≥ 4 adverse events were observed. A randomized trial comparing afatinib plus bevacizumab with single-agent afatinib is ongoing. ■

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Exploring synergy between anti-angiogenic drugs and immunotherapy

In the setting of non-squamous advanced NSCLC without actionable driver mutations, the advent of immune checkpoint inhibitor therapy has led to the implementation of new standards. Synergistic effects can be expected from anti-angiogenic treatment. The vascular endothelial growth factor (VEGF) has been shown to create an immunosuppressive tumor microenvironment by modifying immune cell function besides promoting angiogenesis [1-3]. These mechanisms are likely to contribute to immune checkpoint inhibitor resistance but can be antagonized using agents such as the triple angiokinase inhibitor nintedanib. The angio-immunogenic switch describes the restitution of an immunosupportive tumor microenvironment based on vessel normalization and improved access of immune cells to the tissue [4].

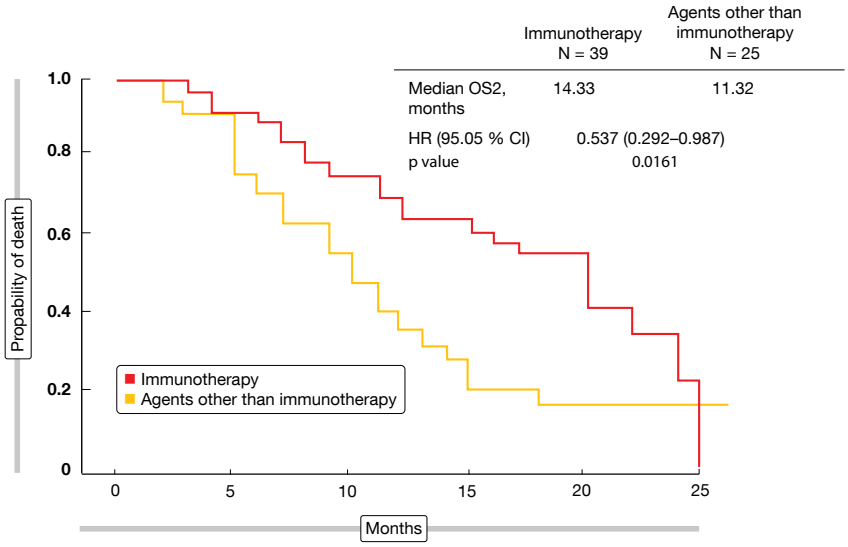

Figure: Time from initiation of docetaxel/nintedanib to progression or death during third-line treatment with immunotherapy or other agents

VARGADO: nintedanib after immunotherapy

Evidence that might provide guidance regarding the selection of treatment after progression on immune checkpoint inhibitor therapy has been obtained from the German non-interventional, prospective VARGADO trial. VARGADO is evaluating nintedanib plus docetaxel after first-line chemotherapy in routine care. The study comprises three cohorts, among them Cohort B in which patients are treated with frontline chemotherapy followed by immune checkpoint inhibition in the second line and nintedanib/docetaxel in the third. Grohé et al. presented data from an updated interim analysis of Cohort B (n = 32) at ESMO 2019 [5].

After a median follow-up of 6.9 months for nintedanib/docetaxel, median PFS was 7.1 months in the third-line setting. Best overall response data were available for 24 patients, with partial responses occurring in 50 % **(Table)**. The disease control rate was 79 %. Overall, this updated analysis of VARGADO continued to demonstrate the clinical benefit of nintedanib plus docetaxel in patients who progressed on immunotherapy. Overall survival data are not mature yet. The authors noted that rational sequencing of an anti-angiogenic agent after immune checkpoint inhibition might be a promising treatment approach in this patient population that warrants further investigation.

TABLE
Outcomes obtained with third-line nintedanib/docetaxel in VARGADO

Progression-free survival (months)	7,1
Objective response (%)	50
Complete response (%)	0
Partial response, n (%)	50
Stable disease (%)	29
Disease control rate (%)	79
Progressive disease (%)	21

SENECA: immunotherapy after nintedanib

A similar setup was analyzed based on data obtained by the open-label, phase IIb SENECA trial. This Italian real-world study tested two docetaxel schedules (33 mg/m^2 on days 1 and 8 three-weekly; 75 mg/m^2 on day 1 three-weekly) along with continuous oral nintedanib in patients with advanced non-squamous NSCLC who had progressed after first-line chemotherapy. Nintedanib maintenance was administered in case of disease control. The final analysis (n = 170) confirmed the efficacy of second-line nintedanib/docetaxel irrespective of the duration of the relapse-free interval after first-line chemotherapy and the docetaxel schedule, with similar OS and PFS findings in both dosing groups [6].

The data presented at ESMO 2019 focused on the effects of second-line nintedanib/docetaxel on subsequent im-

munotherapy in SENECA [7]. Post-progression outcomes were assessed in 64 patients (37.6 % of the entire study population) for those who received third-line treatment with immune checkpoint inhibitors (nivolumab, atezolizumab, pembrolizumab; n = 39) *versus* those treated with other third-line agents (gemcitabine, vinorelbine, erlotinib, crizotinib, cabozantinib; n = 25). The primary endpoints were PFS2 and OS2, the latter of which was defined as the time from the start of docetaxel/nintedanib treatment to progression during third-line therapy or death. According to the analysis, PFS2 did not differ between patients who received immunotherapy and those who did not (10.78 vs. 7.91 months; HR, 0.602; p = 0.0821). However, for OS2, the immunotherapy-treated group fared significantly better (14.33 vs. 11.32 months; HR, 0.537; p = 0.0161; **Figure**). As the authors pointed out, the survival benefit observed with the sequence of docetaxel/nintedanib and immunotherapy became apparent despite the small sample size of this analysis. The synergism between antiangiogenic agents and immunotherapy might be an attractive basis for the development of new therapeutic algorithms. ■

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Innovations in the setting of rare mutations: ALK, ROS1, NTRK, NRG1

BFAST: blood-based NGS as a stand-alone test

Oncogene-directed treatment requires molecular testing, but, as is known, limitations related to tissue collection and tissue-based testing can represent a serious obstacle in clinical practice. Blood-based next generation sequencing (NGS) has the potential to overcome some of these limitations. Therefore, the global, phase II/III, multi-cohort BFAST study was initiated with the aim of prospectively evaluating the relationship between blood-based biomarkers and the clinical activity of frontline targeted therapies or immunotherapy in advanced NSCLC. Patients were enrolled into specific treatment cohorts using only blood-based NGS testing, to establish its clinical utility as a stand-alone test. Biomarkers that were identified included *ALK*, *RET*, *ROS1*, and tumor mutational burden **(Figure)**. BFAST is the first prospective trial to use blood-based NGS testing as the sole method of identifying actionable genetic alterations and assigning NSCLC patients to targeted agents or immunotherapy.

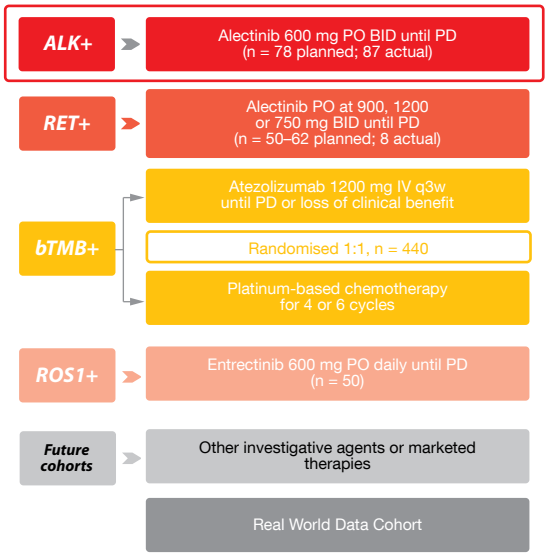

Figure: Cohorts treated in the BFAST trial. bTMB, blood tumor mutational burden

At ESMO 2019, Gadgeel et al. presented the results for the *ALK*-positive cohort [1]. For this group, it was intended to demonstrate consistency of activity of the ALK inhibitor alectinib with the results obtained in the global ALEX trial where tissue-based assess-

ment had been used for patient selection [2]. Within the total screened population (n = 2,219), the 5.4 % prevalence of *ALK* translocation corresponded to the expected rate of 5 % [3]. Eighty-seven patients whose baseline characteristics resembled those of the population treated with alectinib in the ALEX trial entered the cohort and received alectinib 600 mg twice daily.

Confirmed ORR by investigator was defined as the primary endpoint. This was indeed achieved with ORRs of 87.4 % and 92.0 % according to investigator and independent review facility (IRF), respectively, that even exceeded the confirmed ORR of 72.4 % observed in ALEX [4]. Eleven patients (12.6 %) experienced complete remissions according to IRF. The presence of baseline CNS metastases did not affect response rates. In the group of confirmed responders, the event-free rate was 90.4 % at 6 months. Median PFS had not been reached yet at the time of the analysis, with the 12-month PFS rate being 78.38 %. The safety profile of alectinib was consistent with that established in previous phase III trials and post-marketing experience. Overall, these results demonstrated the clinical utility of blood-based NGS as a method to inform clinical decision making in patients with *ALK*-positive NSCLC.

Final PFS data from the ALEX trial

The global, randomized, phase III ALEX study was conducted to compare the efficacy and safety of alectinib *versus* crizotinib in 303 patients with treatment-naïve, *ALK*-positive advanced NSCLC. Mok et al. reported mature PFS and updated OS data after a median follow-up of 37.8 months with alectinib and 23.0 months with crizotinib [4].

According to this analysis, median investigator-assessed PFS was 34.8 and 10.9 months for alectinib and crizotinib, respectively (HR, 0.43; p < 0.0001). The PFS benefit was consistent in patients with and without baseline CNS metastases (HRs, 0.37 and 0.46, respectively). In the alectinib group, patients showed higher event-free rates with respect to PFS regardless of the presence or absence of baseline CNS metastases. At 4 years, 43.7 % of the entire alectinib-treated cohort were event-free, while this applied to none of the patients in the crizotinib arm.

Overall survival data remained immature; here, 4-year rates were 64.5 % and 52.2 % for alectinib and crizotinib, respectively. The confirmed ORRs of 72.4 % vs. 60.9 % remained consistent with the results from the primary data cut-off [2]. Considering the difference in median treatment duration (27.7 vs. 10.8 months), alectinib continued to show a favorable safety profile compared with crizotinib. The authors concluded that this analysis confirms the superior efficacy of alectinib in untreated *ALK*-positive NSCLC patients.

TABLE
Response rates observed in patients with *NTRK*- and *ROS1*-positive NSCLC who received entrectinib

Responders, n (%)	Patients with *ROS1*-positive tumors (n = 53)	Patients with *NTRK*-positive tumors (n = 10)
Objective response	42 (79.2)	7 (70.0)
Complete response	5 (9.4)	1 (10.0)
Partial response	37 (69.8)	6 (60.0)
Stable disease	1 (1.9)	1 (10.0)
Progressive disease	4 (7.5)	0
Non-complete/partial response	2 (3.8)	0
Missing/not evaluable	4 (7.5)	2 (20.0)

Entrectinib in *NTRK*-positive disease

Neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions act as oncogenic drivers and occur in approximately 0.3 % of solid tumors, among them lung cancer [5]. The TRKA/B/C, ROS1 and ALK inhibitor entrectinib has been designed to work in tumors with *NTRK* gene fusions, both at a systemic level and inside the CNS. The accelerated FDA approval of entrectinib for the treatment of adult patients with solid tumors that harbor *NTRK* gene fusions was based on the results from an integrated analysis of three phase I/II trials conducted at more than 150 sites in 15 countries: ALKA-372-001, STARTRK-1, and STARTRK-2 [6]. All of these studies included patients with *NTRK*-, *ROS1*- or *ALK*-positive tumors.

At ESMO 2019, Rolfo et al. presented updated data from the integrated analysis after an additional follow-up of 5 months [7]. The efficacy-evaluable population included 54 patients with advanced *NTRK*-positive solid tumors, among them 10 individuals with lung cancer. At the time of the analysis, ORR remained high at 59.3 %, with four complete remissions (7.4 %). Responses lasted for a median of 12.9 months. Median PFS and OS were 11.8 and 23.9 months, respectively. Systemic response rates did not differ according to baseline CNS disease status. The authors noted that both OS and duration of response were longer than reported in the previous analysis [6].

In patients who had baseline brain metastases, entrectinib gave rise to clinically meaningful and durable benefits. Intracranial ORR and PFS were 54.5 % and 14.3 months, respectively, and median intracranial response had not been reached yet.

The *ROS1*-rearranged treatment group

De Braud et al. reported updated results from the integrated analysis of the ALKA-372-001, STARTRK-1 and STARTRK-2 trials that focused on lung cancer patients [8]. Out of 63 individuals, 53 and 10 had *ROS1*-positive and *NTRK*-positive lung cancer, respectively. ORRs were 79.2 % and 70.0 %, respectively, for these two cohorts **(Table)**. Complete responses occurred in approximately 10 % in each group. In the *ROS1*-positive population, median duration of response was 24.6 months; median PFS amounted to 19.0 months, and median OS had not been reached yet.

Clinically meaningful and durable responses were observed in *ROS1*-positive patients with brain metastases (ORR, 73.9 %; median duration of response, not estimable) as well as those

without (ORR, 83.3 %; median duration of response, 24.6 months). The cohort with baseline CNS lesions responded intracranially in 55 %. Here, responses lasted for a median of 12.9 months, and intracranial PFS was 7.7 months. Both analyses of STARTRK-2, STARTRK- and ALK-372-001 revealed good tolerability of entrectinib, with a safety profile consistent with that previously reported.

NRG1 fusion: clinical experience with afatinib

Various types of tumors harbor actionable *NRG1* gene fusions that were shown to increase cell proliferation through ErbB signaling and may function as oncogenic drivers [9–11].

The estimated overall prevalence of these fusions across solid tumors is approximately 0.2 % but was reported to be up to 31 % in invasive mucinous adenocarcinoma of the lung [11, 12]. Based on the involvement of ErbB signaling pathways in *NRG1*-positive tumors, the pan-ErbB family blocker afatinib is a potential treatment option in these patients. Liu et al. presented seven case reports including four lung cancer cases that support this assumption [13]. Three patients were treated for non-mucinous adenocarcinoma of the lung, and one for invasive mucinous adenocarcinoma. All of them had had several treatment lines before being prescribed afatinib, with one patient even receiving 14 lines of previous therapy.

Partial responses were achieved as best overall responses in three individuals and proved durable (duration of best response, 18 to 24 months), with treatment ongoing in two cases. One patient obtained stable disease that lasted 4 months. According to the conclusion of the authors, these findings add to the growing body of evidence showing that afatinib is a potential treatment option for patients with *NRG1*-fusion–positive tumors, particularly in the absence of other driver aberrations. Molecular testing would be of particular importance in invasive mucinous adenocarcinoma of the lung where *NRG1* fusion prevalence is relatively high. ■

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CNS disease does not preclude successful treatment

Neurological symptom burden at diagnosis affects survival

Brain metastases occur in approximately 35 % of patients with metastatic NSCLC and are associated with a variety of neurological symptoms, as well as poor prognosis [1]. However, little is known about the prognostic impact of the symptomatic burden of CNS lesions at the time of diagnosis. This was assessed by an analysis based on a real-life cohort of 1,608 NSCLC patients from the Vienna Brain Metastasis Registry with newly diagnosed brain metastases [2]. Neurological symptoms were evident in 73.8 %. Symptoms included neurological deficits (61.3 %), signs of increased intracranial pressure (30.3 %), epileptic seizures (13.6 %), and neuropsychological symptoms (14.5 %).

According to this analysis, oligosymptomatic or asymptomatic patients, compared to symptomatic patients, experienced significantly longer median OS after their diagnosis of brain metastases (11 vs. 7 months; $p < 0.001$). Interestingly, signs of increased intracranial pressure showed a significant correlation with prolonged survival (8 vs. 6 months in patients without increased intracranial pressure; $p = 0.032$). A multivariate analysis identified an independent association between the presence of neurological symptoms and survival from the time of diagnosis. Overall, this study highlights the importance of integrating the neurological symptom burden into the prognostic assessment of patients with NSCLC and brain metastases.

Outcomes according to CNS disease: single-agent pembrolizumab …

The KEYNOTE-001, 010, 024, and 042 trials compared pembrolizumab mono-

TABLE 1
Outcomes for pembrolizumab plus chemotherapy *versus* chemotherapy alone in NSCLC patients with and without brain metastases at baseline

	Patients with brain metastases		Patients without brain metastases	
	Pembrolizumab + chemotherapy (n = 105)	Chemotherapy (n = 66)	Pembrolizumab + chemotherapy (n = 643)	Chemotherapy (n = 484)
Median overall survival, months	18.8	7.6	22.5	13.5
HR for OS	0.48		0.63	
Median progression-free survival, months	6.9	4.1	8.8	5.3
HR for PFS	0.44		0.55	
Overall response rate, n (%)	41 (39.0)	13 (19.7)	351 (54.6)	154 (31.8)
Median duration of response, months	11.3	6.8	12.2	6.0
Duration of response ≥ 12 months, n (%)[a]	15 (45.7)	0 (not reached)	101 (50.8)	21 (37.0)

therapy with chemotherapy in NSCLC patients [3-6]. A pooled analysis of these four studies was performed to investigate the effects of pembrolizumab in PD-L1–positive disease according to the presence of brain metastases at baseline [7]. Exploratory subgroup analyses for patients with CNS lesions had been prespecified in all trials. Mansfield et al. presented data for a total of 3,170 individuals 293 of whom had brain metastases (199 and 94 of these received pembrolizumab and chemotherapy, respectively), while 2,877 showed no cerebral disease (pembrolizumab: n = 1,754; chemotherapy: n = 1,123). Approximately half of the patients in each treatment group had a tumor proportion score (TPS) ≥ 50 %.

The clinical benefit of pembrolizumab in patients with TPS ≥ 50 % was similar irrespective of the presence of brain metastases at baseline. Median OS was 19.7 vs. 9.7 months for the pembrolizumab and chemotherapy arms in patients with CNS lesions (HR, 0.78), and 19.4 vs. 11.7 months in those without (HR, 0.66). Comparable risk reductions resulted for PFS, with 4.1 vs. 4.6 months in patients with brain metastases (HR, 0.70) and 6.5 vs. 6.1 months in those without (HR, 0.69). Likewise, in the group with TPS ≥ 1 %, pembrolizumab gave rise to similar OS and PFS effects.

Response rates measured at all tumor sites were higher with pembrolizumab than with chemotherapy for patients with and without brain metastases. In the group with cerebral lesions, median duration of response had not been reached yet for pembrolizumab-treated patients with both TPS ≥ 50 % and TPS ≥ 1 %, while it was 7.6 and 8.3 months, respectively, with chemotherapy. Pembrolizumab monotherapy showed a manageable safety profile irrespective of the presence of brain metastases. In their conclusion, the authors emphasized that prembrolizumab monotherapy is a standard-of-care therapy for patients with PD-L1–positive advanced NSCLC including those with treated, stable brain metastases.

… and pembrolizumab plus chemotherapy

In similar vein, Powell et al. reported an exploratory pooled analysis of the KEYNOTE-021, 189, and 407 trials that evaluated the outcomes in NSCLC patients with and without stable brain metastases at baseline [8]. These studies had tested first-line pembrolizumab plus platinum-based chemotherapy compared to chemotherapy [9-12]. Among a total of 1,298 patients, 171 had brain metastases at the time of study inclusion (pembrolizumab plus chemotherapy: n = 105; chemotherapy: n = 66) and 1,127 did not (pembrolizumab plus chemotherapy: n = 643; chemotherapy: n = 484).

Pembrolizumab plus chemotherapy improved outcomes over chemotherapy alone in both groups **(Table 1)**. This was true for OS, PFS, ORR, and duration of response. The combination had a manageable safety profile in patients with and without brain metastases. In the experimental arm, the presence of cerebral lesions was not associated with an increased rate of adverse events affecting the CNS. The authors noted that pembrolizumab plus chemotherapy is a standard-of-care strategy for patients with advanced NSCLC including those with treated and untreated asymptomatic brain metastases.

GIDEON: real-world experience with afatinib

In patients with *EGFR* mutations, the proportion of NSCLC patients who de-

TABLE 2
Clinical efficacy of afatinib in patients with *EGFR*-mutant NSCLC with and without baseline brain metastases

	Patients with brain metastases	Patients without brain metastases
12-month overall survival rate, %	78.1	76.9
Median progression-free survival, months	10.6	16.0
12-month progression-free survival rate, %	43	60
Overall response rate, %	74	73
Disease control rate, %	91	90

velop brain metastases is as high as 40 % to 60 % [13-15]. A subanalysis of the non-interventional German GIDEON study that prospectively assessed the real-world use of afatinib in the setting of *EGFR*-mutant advanced NSCLC demonstrated activity of this treatment in patients with baseline brain metastases [16]. GIDEON included 49 patients with cerebral lesions (32.5% of the total population). Notably, this proportion is higher than in the randomized controlled trials conducted with afatinib [17, 18].

The presence or absence of brain metastases had no influence on ORR or DCR **(Table 2)**. In line with the negative prognostic impact of CNS lesions, median PFS was shorter in patients with brain metastases than in those without (10.6 vs. 16.0 months). Median OS had not been reached yet at the time of the analysis. The safety results were consistent with those reported in the pivotal LUX-Lung clinical trials [18-20], and adverse events occurring during afatinib treatment did not differ across patients with and without brain metastases. Taken together, these data underline the efficacy and safety of afatinib in patients with CNS lesions, thus supporting the use of afatinib in this treatment setting. ■

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Interview: Stephen Liu, MD, Lombardi Comprehensive Cancer Center at Georgetown University, Washington, DC, USA

Even infrequent actionable drivers are important

Where are we today regarding the clinical evaluation of *NRG1*-directed therapies?

NRG1 fusions are oncogenic events, i.e., transforming events that occur in all tumor types, although in fairly low frequencies. Their prevalence is less than 1 % throughout all tumor types. Some reports have estimated the *NRG1* fusion prevalence at approximately 0.2 % [1]. Although *NRG1* fusions are not a common event, they represent an important actionable driver. On the cell level, what happens is that the *NRG1* fusion partner provides a transmembrane anchor for the EGF-like domain of NRG1. This EGF domain then serves as a ligand that interacts with HER3 or HER4, which will heterodimerize and induce signaling through phosphorylation via the MAPK/PI3K pathways.

At ESMO 2019, we saw some early signs of drug activity in *NRG1*-positive lung cancer with updates on several prospective trials in progress or in the planning stages. With the pan-ErbB TKI afatinib, clear responses have been observed in previous case reports, reinforced by an updated case series presented at ESMO 2019 [2]. Of course, given the nature of these reports, this does not actually inform us with respect to the response rate, but what it does tell us is that *NRG1* fusions are actionable drivers, and it demonstrates the major characteristics that we are looking for in viable therapeutic targets: rapid responses, potentially durable responses, and dramatic responses. This is a clear target, and when we identify it, we should act upon it. Several trials are in development, and hopefully in the years

to come we will see the results obtained in patients with these rare but important events.

Will there be any novel molecular targets for lung cancer treatment in the foreseeable future?

The molecular targets established in the treatment of NSCLC do indeed guide our initial therapy. Approved agents are available for *EGFR*-, *ALK*-, *ROS1*-, *BRAF*- and *NTRK*-positive disease. What we have recently seen is the emergence of *RET* fusions as a clear actionable driver. Hopefully, highly selective RET kinase inhibitors such as selpercatinib and pralsetinib (BLU-667) will reach approval for the treatment of *RET*-positive tumors soon. *MET* exon 14 skipping mutations, *EGFR* exon 20 mutations and *HER2* insertions are clearly actionable drivers. We do not have FDA-approved drugs for these targets yet, but we certainly will in the near future. For the treatment of lung cancer with *NRG1* fusions, prospective studies that show efficacy of targeted agents are still lacking, but they will come.

We can assume that there are more oncogenic driver aberrations out there, although they will be harder to find, as they will probably be less common than those we already have. However, it is important to identify these drivers, because they affect the tumor biology and will help select for targeted therapy and, importantly, potentially de-select for immunotherapy. ■

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Emerging survival benefits in the small-cell setting

IMpower133: updated OS results

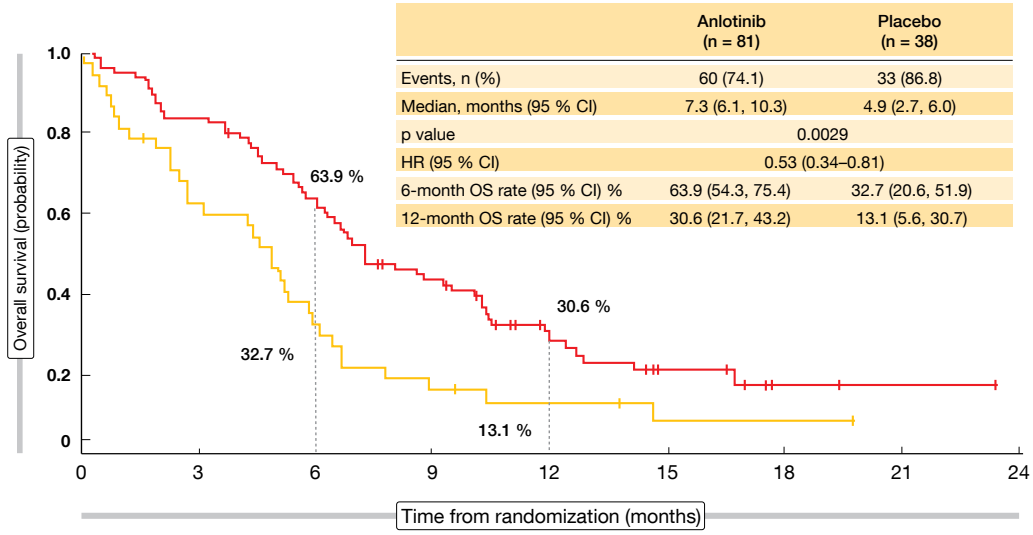
Given the dismal prognosis of patients with extensive-stage small-cell lung cancer (ES-SCLC), there is a high need of effective first-line treatment options. The global, double-blind, randomized, placebo-controlled, phase I/III IMpower133 study was the first trial to demonstrate survival benefits in ES-SCLC with the PD-L1 inhibitor atezolizumab plus carboplatin and etoposide compared to placebo plus chemotherapy [1]. Median OS was 12.3 vs. 10.3 months in the two treatment arms (HR, 0.70; p = 0.007), along with a tolerable safety profile. Based on these results, atezolizumab plus carboplatin and etoposide received approval for the first-line treatment of patients with ES-SCLC.

Reck et al. presented updated OS findings of IMpower133 after an additional follow-up of 9 months (median follow-up, 22.9 months) [2]. In the ITT population, atezolizumab plus chemotherapy gave rise to continuous OS improvement (median, 12.3 vs. 10.3 months; HR, 0.76; p = 0.0154). The landmark analysis at 18 months demonstrated a survival advantage of 13 % in the experimental arm (34.0 % vs. 21.0 %). According to the conclusion of the authors, these results further support the combination of atezolizumab with chemotherapy as the new standard of care for untreated ES-SCLC in an all-comer patient population.

Additional analyses of CASPIAN and IMpower133

Similarly, the global, randomized, open-label, phase III CASPIAN study has shown statistically significant improvement in OS with first-line durvalumab plus etoposide plus platinum-based chemotherapy (EP) versus EP alone in patients with treatment-naïve ES-SCLC (median OS, 13.0 vs. 10.3 months; HR, 0.73; p = 0.0047) [3]. No additional toxicity was noted. At ESMO 2019, Paz-Ares et al. reported patterns of first progression and patient-reported outcomes in the CASPIAN trial [4]. The analysis indicated that numerically fewer patients in the durvalumab-treated arm developed new lesions at first progression compared to the control arm (41.4 % vs. 47.2 %). However, no difference was found for new brain/CNS lesions (11.6 % vs. 11.5 %). In line with the efficacy outcomes, all patient-reported outcomes including time to deterioration for all symptoms, functioning, and health-related quality of life favored durvalumab plus EP compared with EP alone.

Both IMpower133 and CASPIAN analyzed survival based on biomarker expression. The exploratory analysis of IMpower133, which included PD-L1 immunohistochemistry and assessment of blood tumor mutational burden, suggested that patients derive OS benefit from the addition of atezolizumab regardless of biomarker status [2]. However, PD-L1 assessments were based on a limited data set, as only 34 % of the ITT population were PD-L1–evaluable. Likewise, CASPIAN showed no significant interaction of PD-L1 expression with clinical outcomes [4]. The PD-L1 status was evaluable in 51.6 % of patients. PD-L1 expression was low, with 94.9 % and 77.6 % showing levels < 1 % on tumor cells and immune cells, re-



	Anlotinib (n = 81)	Placebo (n = 38)
Events, n (%)	60 (74.1)	33 (86.8)
Median, months (95 % CI)	7.3 (6.1, 10.3)	4.9 (2.7, 6.0)
p value	0.0029	
HR (95 % CI)	0.53 (0.34–0.81)	
6-month OS rate (95 % CI) %	63.9 (54.3, 75.4)	32.7 (20.6, 51.9)
12-month OS rate (95 % CI) %	30.6 (21.7, 43.2)	13.1 (5.6, 30.7)

Figure: ALTER1202: overall survival advantage with anlotinib over placebo in patients treated with two or more previous lines of chemotherapy

spectively. The authors of both trials concluded that further analyses are needed to evaluate the association of potential biomarkers with clinical outcomes for ES-SCLC patients.

Third line and later lines: anlotinib

The multi-targeted TKI anlotinib works by selectively inhibiting various growth factor receptors that enhance proangiogenic pathways as well as tumor proliferation and are expressed at increased levels in SCLC. The multicenter, randomized, double-blind, phase II ALTER1202 trial assessed anlotinib in patients with limited-stage SCLC or ES-SCLC who had developed progression after ≥ 2 lines of chemotherapy. A previous analysis has shown significantly improved PFS compared to placebo (4.1 vs. 0.7 months; HR, 0.19; p < 0.0001) [5]. At that time, findings with respect to survival had been immature.

According to the updated OS results presented at ESMO 2019, anlotinib was significantly superior to placebo, with median OS of 7.3 vs. 4.9 months (HR, 0.53; p = 0.0029; **Figure**) [6]. Survival rates with anlotinib exceeded those observed for placebo at 6 months (63.9 % vs. 32.7 %) and 12 months (30.6% vs. 13.1 %). Most of the subgroups benefited from the active treatment. Patients with brain metastases showed a 77 % reduction in mortality (median OS, 6.3 vs. 2.6 months; HR, 0.23; p = 0.0009). In this cohort, 55.7 % vs. 0 % were alive at 6 months.

ALTER1202 is the first randomized, double-blind study to demonstrate a survival advantage for patients with relapsed SCLC who have experienced treatment failure after at least two treatment lines. The authors suggested that anlotinib should be considered a new standard of care for patients with SCLC progressing after second-line or later-line chemotherapy. ■

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