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# memo – inOncology SPECIAL ISSUE

## Congress Report ASCO 2019

## A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the ASCO Congress, 31st May – 4th June 2019, Chicago, USA

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# Preface

**Dear Colleagues,**

Lung cancer is still a global public health problem and the first cause of cancer-related mortality everywhere in the world. Nowadays, this has particular implications for elderly patients considering the generally increasing life expectancy in conjunction with the rising cancer incidence with age. At the time of diagnosis, the median age of patients with lung cancer is 70 years in the USA and 65 to 70 years in Europe. Given the multitude of treatment options that are being tested or have already been established in clinical practice, it is safe to say that there is no more room for nihilism with respect to the older age group today. At the same time, the necessity of further improvement of treatment tolerability and personalization is beyond doubt.

At the ASCO 2019 Congress that took place in Chicago from 31st May to 4th June, a multitude of interesting data was presented in the field of lung cancer including (neo)adjuvant strategies and emergent agents for various types of oncogene-driven adenocarcinoma. Immunotherapy has made its way into the frontmost treatment settings; here, convincing evidence has been gained in phase II studies evaluating preoperative checkpoint inhibition. Likewise, the adjuvant armamentarium is expanding, with biomarkers potentially helping to refine patient selection. Long-term results obtained with immunotherapies in metastatic disease demonstrate lasting activity over years in a certain percentage of patients, while additional predictive biomarkers are entering the picture and might contribute to treatment decisions both before the initiation of (chemo)immunotherapy and during the early course of treatment.

In the area of targeted therapies, novel agents as well as combinations of established drugs will most likely define new standards for patients with advanced NSCLC in the years to come. Examples of combined regimens include the addition of anti-angiogenic agents or chemotherapies to EGFR tyrosine kinase inhibitors. Importantly, the range of known rare oncogenic driver mutations is growing, and, along with them, the availability of innovative drugs that selectively and potently target these aberrations. Thanks to dedicated research efforts, the proportion of patients who depend on chemotherapies alone for systemic treatment of their disease is constantly decreasing.

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# Early-stage NSCLC: promising (neo)adjuvant approaches

## The NEOSTAR trial

Effective treatment options are called for in patients with resectable non-small-cell lung cancer (NSCLC), as more than half of those with stage I to III disease experience relapses [1]. Chen et al. demonstrated in their animal model that tumor PD-L1 upregulation is critical for the spread and survival of metastases [2]. Based on these considerations, several clinical trials are investigating the potential benefits of immunotherapies in the neoadjuvant setting.

The randomized phase II NEOSTAR trial included 44 surgical candidates with stage I to IIIA NSCLC [3]. They were randomized to 3 doses of nivolumab 3 mg/kg on days 1, 15, and 29, or the same nivolumab schedule plus ipilimumab 1 mg/kg on day 1. Surgery was performed within 3 to 6 weeks after the last dose. Major pathological response (MPR), i.e., ≤ 10 % viable tumor cells, was defined as the primary endpoint. It was assumed that nivolumab and/or the combination will produce an MPR rate greater than the one achieved with induction chemotherapy as compared to historical controls. Among the 44 randomized patients, who made up the intent-to-treat (ITT) population, 23 received nivolumab alone, and 21 were treated with nivolumab plus ipilimumab. Thirty-nine patients underwent surgical resection.

## Clinical benefits & increased T-cell infiltration

The MPR rate observed in the combination group met the pre-specified trial ef-

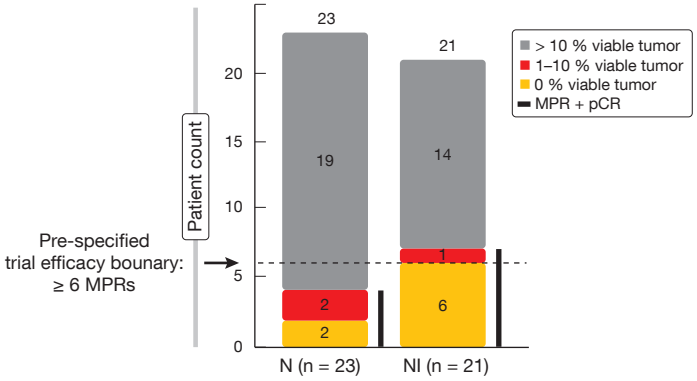


**Figure 1:** NEOSTAR: pathological response rates obtained with nivolumab alone (N) and nivolumab plus ipilimumab (NI)

ficacy boundary. For the ITT population, it was shown that MPRs plus pathological complete responses (pCRs; i.e., 0 % viable tumor cells) occurred in 33 % of patients treated with both nivolumab and ipilimumab **(Figure 1)**. With nivolumab alone, this was 17 %. In the resected population, the combination induced a 44 % MPR plus pCR rate, with pCR accounting for 38 % (MPR plus pCR for nivolumab, 19 %). Overall response rates (ORR) by RECIST according to imaging were 19 % and 22 %, respectively, in the ITT population. One patient in the combination arm (5 %) achieved complete response (CR); in both arms, a total of eight patients (36 %) had partial responses (PRs).

No unacceptable toxicity or increases of perioperative morbidity or mortality were observed. However, the authors noted that nodal immune flares deserve attention in the context of neoadjuvant immunotherapy, as patients might experience seeming radiographic nodal progression due to the emergence of granulomas that need to be distinguished from tumor growth. This is important as potentially curative surgery might be withheld if clinicians fail to differentiate between nodal immune flares and disease progression.

RECIST responses were shown to be positively associated with MPR rates. Elevated baseline PD-L1 expression correlated with radiographic responses and pathological tumor regression. In accordance with the improvement of response rates, immune characterization of surgical samples by flow cytometry revealed that the combined treatment was associated with higher frequencies of CD3-positive tumor-infiltrating lymphocytes as well as tissue resident and effector memory T cells. Moreover, nivolumab plus ipilimumab gave rise to increases of T cell repertoire diversity and reactivity in the tumor.

## Single-agent atezolizumab: LCMC3

The multicenter phase II LCMC3 study is currently assessing the PD-L1 inhibitor atezolizumab in patients with stage IB, II, IIIA and selected IIIB resectable and untreated NSCLC (planned accrual, n = 180). Two cycles of atezolizumab are administered prior to surgery. MPR constitutes the primary endpoint. At the ASCO 2019 Congress, Kwiatkowski et al. presented the results of the efficacy interim analysis [4]. At this time, the safety population comprised 101 patients. Among these, 90 (89 %) underwent surgery and thus represented the intended surgery population. Eighty-four resected patients (83 %) had MPR assessment. After the exclusion of patients with *EGFR*- and *ALK*-positive tumors, the primary efficacy population included 77 individuals (76 %). As many as 46 % of the patients in the safety population had stage IIIA/IIIB disease, and 51 % showed PD-L1 expression.

In the intended surgery population, PR and disease stabilization (SD) were achieved in 7 % and 89 %, respectively. For the primary efficacy population, the MPR rate amounted to 19 %, and 5 % of patients obtained pCRs. Forty-nine percent had ≥ 50 % pathological regression of their specimens. The authors rated these results as encouraging considering the advanced stage of disease in a large proportion of patients. Pathological regression correlated moderately with changes in tumor lesion size according to RECIST. MPR and pathological regression occurred irrespective of PD-L1 expression and tumor mutational burden. Moreover, no significant associations between gene alterations and MPR were observed. Atezolizumab monotherapy was well tolerated, and no new safety signals emerged. As this interim analysis passed its futility boundary, study enrollment continues. IMpower030, a placebo-controlled phase III study investigating atezolizumab combined with platinum-based chemotherapy, is ongoing.

## Chemo-immunotherapy: pCR of 71 %

A combined neoadjuvant approach was tested by the multicenter, single-arm, open-label phase II NADIM study [5]. Patients with resectable stage IIIA NSCLC received 3 cycles of nivolumab 360 mg plus chemotherapy with paclitaxel and carboplatin. Surgery was performed in the third or fourth week after day 21 of the third cycle. Thereafter, adjuvant treatment consisting of nivolumab was administered for a total of one year. The ITT population consisted of 46 patients, with 41 undergoing surgery.

Nivolumab plus chemotherapy proved tolerable. None of the patients withdrew from the study preoperatively due to disease progression or toxicity, and surgery was not delayed in any patient. No intraoperative complications occurred, and postoperative complications were manageable. Neoadjuvant treatment resulted in clinical responses in almost all of the patients. The CR and PR rates amounted to 6.5 % and 72 %, respectively, and SD was observed in 17.5 %. Major pathological responses occurred in 85.36 %. At 71.4 %, the pCR rate was unprecedented. Down-staging was obtained in 93 % of cases.

## JIPANG: adjuvant pemetrexed proves feasible

In the setting of postoperative adjuvant chemotherapy, the randomized JIPANG trial attempted to answer the question of which cisplatin-based regimen is most effective [6]. Patients with completely resected non-squamous stage II to IIIA NSCLC were randomized to either pemetrexed plus cisplatin (n = 389) or

  

vinorelbine plus cisplatin (n = 395). Each regimen was administered for up to 4 cycles. JIPANG was the first phase III trial to assess pemetrexed plus cisplatin as a postoperative adjuvant regimen.

For recurrence-free survival (RFS), which was defined as the primary endpoint, the trial showed no superiority of pemetrexed plus cisplatin. However, the two regimens demonstrated similar efficacy (median RFS, 38.9 vs. 37.3 months with pemetrexed plus cisplatin vs. vinorelbine plus cisplatin; HR, 0.98). Similarly, OS did not differ across the arms (HR, 0.98). The RFS-related subgroup analysis suggested that patients with *EGFR* mutations fared better with the vinorelbine regimen, while those with *EGFR* wild-type derived greater benefit from the pemetrexed-based treatment **(Figure 2)**.

At the same time, pemetrexed plus cisplatin showed higher tolerability. A greater proportion of patients completed 4 cycles of treatment (87.9 % vs. 72.7 %), and toxicity was milder, with lower rates of serious and grade 3 to 5 adverse events (AEs). Severe hematological AEs occurred significantly less frequently (24.7 % vs. 81.8 %; p < 0.001), and the treatment discontinuation rate was lower (9.5 % vs. 23.5 %). Based on these data, pemetrexed plus cisplatin can be an option for postoperative adjuvant chemotherapy in stage II to IIIA non-squamous NSCLC, especially for patients with *EGFR* wild-type disease.

## Postoperative EGFR TKI treatment

The role of adjuvant EGFR tyrosine kinase inhibitor (TKI) therapy in early-stage *EGFR*-mutant NSCLC is still controversial. In their meta-analysis of 11 trials including a total of 1,152 resected NSCLC patients with activating *EGFR* mutations, Tang et al. found that when compared to treatment without adjuvant EGFR TKIs, EGFR TKIs prolonged both OS (OR, 0.63; p = 0.004) and disease-free survival (DFS; OR, 0.56; p < 0.00001) [7]. Predefined subgroup analyses suggested a greater DFS benefit with EGFR TKIs than with chemotherapy. However, this did not apply to OS. Compared to chemotherapy alone, the combination of EGFR TKI treatment and chemotherapy resulted in significantly longer DFS (OR, 0.48; p < 0.00001) and OS (OR, 0.50; p = 0.003). In addition, TKI-treated patients showed fewer grade ≥ 3 AEs than the chemotherapy-treated cohorts (OR, 0.22; p < 0.00001). Considering these findings, adjuvant EGFR TKIs are a potential treatment option as single agents or combined with chemotherapy in patients with completely resected *EGFR*-positive NSCLC.

Alterations of the tumor microenvironment (TME) might help inform patient selection with respect to adjuvant EGFR TKI treatment. Khalil et al. identified 8 key TME genes whose high expression was associated with improved DFS in patients with *EGFR* mutations [8]. The researchers clustered them in two groups characterized by distinct immune profiles. One group showed a more "inflamed" phenotype (e. g., higher lymphocyte infiltration score and TGF-β response) than the other. Both DFS and disease-specific survival were significantly longer in the inflamed group than in the non-inflamed group. The results suggest that patient stratification according to these genes could contribute to identifying individuals who will benefit from adjuvant therapy.

## Three months vs. 2 years of afatinib

As the optimal duration of adjuvant EGFR TKI treatment is under debate, a randomized phase II trial assessed the daily administration of afatinib for 2 years (n = 22) *versus* 3 months (n = 24) in patients who had completed standard adjuvant treatment after resection of stage I to III NSCLC [9]. The study was closed at 46 of 60 planned patients for slow accrual. DFS at 2 years was defined as the primary endpoint. Here, the 2-year regimen induced a 14 % reduction of recurrence rates compared to the 3-month schedule (DFS at 2 years, 85 % vs. 71 %), although this difference was not statistically different. Median DFS and OS have not been reached in either arm yet.

As in prior trials of adjuvant EGFR TKIs, many patients in the 2-year arm did not complete treatment, with withdrawal of consent being the main rea-

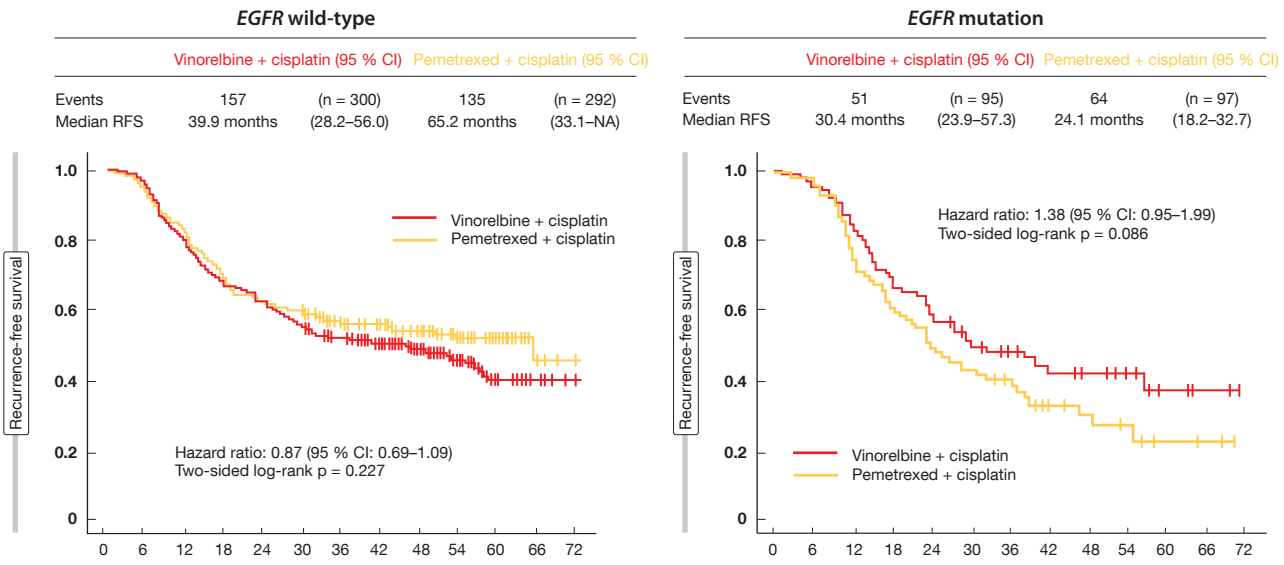


**Figure 2:** Greater relapse-free survival benefit with pemetrexed plus cisplatin in *EGFR* wild-type patients, and with vinorelbine plus cisplatin in patients with *EGFR* mutations

son (23 %), followed by toxicity (18 %) and recurrence (9 %). The authors concluded that in the era of TKIs with improved tolerance, the duration of adjuvant therapy remains an important question.

## Personalization of consolidation immunotherapy

Moding et al. investigated the use of circulating tumor DNA (ctDNA) for the detection of molecular residual disease after chemoradiation therapy (CRT) in patients with localized NSCLC [10]. The scientists hypothesized that consolidation immune checkpoint inhibition (CICI) after CRT, which gives rise to additional toxicity and costs, might be omitted in patients with undetectable ctDNA. Samples were collected from 62 patients with stage IIB to IIIB NSCLC who received concurrent CRT with curative intent. CICI was administered in 25 of these.

Indeed, the presence of ctDNA was shown to have predictive power. In the group without detectable ctDNA after CRT, median freedom from progression (FFP) had not been reached yet at the time of analysis; these patients have an excellent prognosis and might not benefit from CICI. Reassessments during the early CICI phase demonstrated that ctDNA changes might identify responders and non-responders to consolidation therapy. Median FFP had not been reached yet in patients without detectable ctDNA during early CICI. In those who showed ctDNA decreases, median FFP was 16.5 months; this group did not experience progression and thus appeared to benefit from immunotherapy **(Figure 3)**. Patients who had ctDNA increases after the start of consolidation fared worst, with a median FFP of 0.4 months. Here, rapid progression indicated a lack of response to treatment.

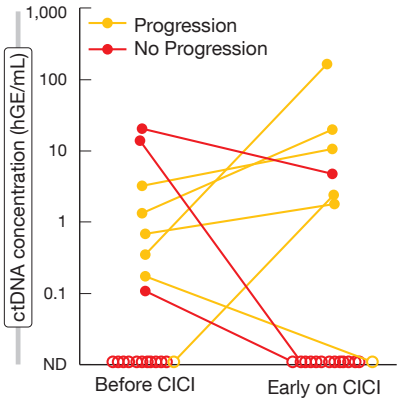


**Figure 3:** Association between changes in ctDNA levels and clinical course in patients receiving immune checkpoint inhibitor consolidation (CICI) after adjuvant chemoradiation

The authors proposed an algorithm including the initiation of CICI after CRT only if ctDNA is present. Early after the start of CICI, another analysis would be conducted that prompts either a change in treatment or the continuation of immunotherapy depending on the persistence of ctDNA. Patients who do not show detectable ctDNA after CRT would not receive CICI but undergo ctDNA surveillance in addition to imaging. Nevertheless, prospective clinical trials will be essential to establish the ability of the ctDNA analysis to personalize consolidation immunotherapy. ■

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# Novel first-line options and other insights in *EGFR*-mutant lung cancer

## RELAY: addition of ramucirumab

Although treatment with EGFR TKIs is generally efficient in patients with *EGFR*-mutant lung cancer, resistance inevitably develops within 8 to 12 months of the initiation of therapy, leading to treatment failure. Therefore, there is an unmet need for options that extend the activity of EGFR-targeted therapies. Dual blockade of the VEGF and EGFR signaling pathways represents a potential approach in this respect.

The global, randomized, placebo-controlled phase III RELAY trial tested the combination of the first-generation EGFR TKI erlotinib with the anti-VEGFR-2 antibody ramucirumab as first-line strategy in patients with stage IV, *EGFR*-mutation–positive (i.e., exon 19 deletion, exon 21

  

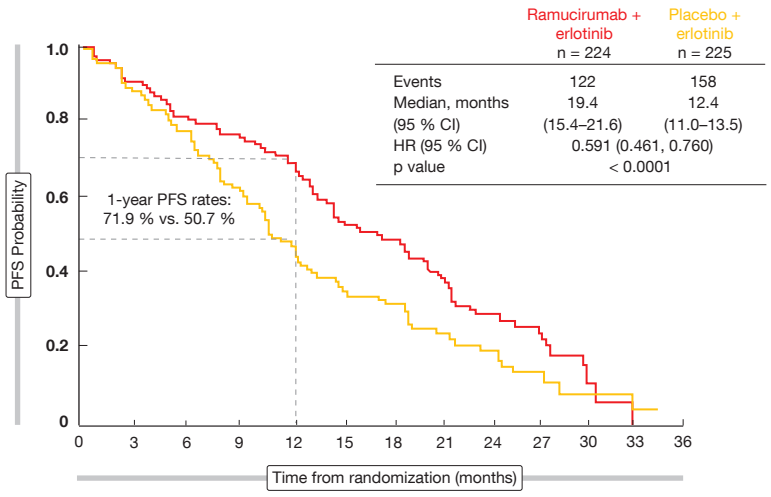


**Figure:** Seven-month PFS improvement with the addition of ramucirumab to erlotinib in the RELAY trial

L858R mutation) NSCLC [1]. Patients with brain metastases were excluded. The treatment consisted of either erlotinib 150 mg/d plus ramucirumab 10 mg/kg every 2 weeks (n = 224) or erlotinib 150 mg/d plus placebo (n = 225). Treatment was continued until progression or unacceptable toxicity. Investigator-assessed PFS constituted the primary endpoint. Hundred centers in 13 countries participated in the study. In both arms, 77 % of patients were Asian.

The addition of ramucirumab led to a significant 7-month PFS improvement that translated into a highly statistically significant risk reduction of 41 % (19.4 vs. 12.4 months; HR, 0.591; p < 0.0001; **Figure**). The Kaplan Meier curves separated from the beginning. At 1 year, 71.9 % vs. 50.7 % of patients were progression-free. Independent blinded central review showed a consistent PFS benefit (HR, 0.671; p = 0.0022). Ramucirumab plus erlotinib gave rise to PFS benefits across most of the subgroups. Notably, patients with exon 19 deletions and exon 21 L858R mutations derived similar benefits (HRs, 0.651 and 0.618, respectively).

## Secondary endpoints

Overall response rates were comparable across the two arms (76 % vs. 75 %), which also applied to disease control rates (95 % vs. 96 %). However, duration of response was significantly longer with the ramucirumab-based regimen (18.0 vs. 11.1 months; HR, 0.619). OS outcomes are still immature. For PFS2, i.e. the time from randomization to second disease progression, the analysis revealed a significant advantage for the combination (HR, 0.690; p = 0.03). This implies freedom from progression as well as an OS benefit. The incidence of the *EGFR* T790M resistance mutation was assessed using liquid biopsy at baseline and one month later. While no T790M mutations were detected at baseline in either group, mutation rates at 30 days in patients experiencing progression were similar at 43 % vs. 47 %.

The safety results were consistent with the established profiles for erlotinib and ramucirumab. Grade ≥ 3 treatment-emergent AEs occurred more frequently in the combination arm (72 % vs. 54 %). However, discontinuation rates for all study treatments due to AEs did not differ (13 % vs. 11 %). Any-grade and severe hypertension was more prevalent in the experimental arm, although there were no cases of grade 4 hypertension. Similarly, ramucirumab-treated patients more frequently developed elevations of transaminases, but most events were rated as grade 1 or 2. This also applied to bleeding events. Overall, these findings suggest that erlotinib plus ramucirumab is a new option for the initial treatment of patients with *EGFR*-mutant metastatic NSCLC.

## Gefitinib plus chemotherapy

Another strategy to delay or prevent acquired resistance to first-line EGFR TKI therapy is the combination of oral TKIs with chemotherapy. At the ASCO 2019 Congress, Noronha et al. presented the results of a randomized, open-label phase III trial comparing the first-generation EGFR TKI gefitinib with gefitinib plus pemetrexed/carboplatin for four cycles followed by pemetrexed maintenance in patients with non-progressive disease [2]. Patients with stage IIIB or IV, *EGFR*-mutant NSCLC received either the combination (n = 174) or the gefitinib monotherapy (n = 176) with first-line palliative intent until progression. More than 20 % of patients in each arm had ECOG PS 2. In 17 % and 19 %, respectively, brain metastases were present. Patients with rare *EGFR* aberrations, such as exon 18 and exon 20 mutations, were included.

The combined approach induced significant improvements compared to gefitinib alone regarding both PFS and OS. Median PFS, which was defined as the primary endpoint, was doubled (16 vs. 8 months; HR, 0.51; p < 0.0001). Significant PFS benefits occurred across all of the subgroups. Concerning OS, the mortality risk was reduced by 55 % (not reached vs. 17 months; HR, 0.45; p < 0.0001). The patients in the combined arm also showed more pronounced responses (ORR, 75.3 % vs. 62.5 %; p = 0.01) and median depth of response (-56.4 vs. -43.5; p = 0.002). Clinically relevant grade ≥ 3 toxicities doubled from 25.3 % to 50.6 % (p < 0.001). Most of these were cytopenias. Except for nephrotoxicity and hypokalemia, there were no significant increases across the two arms for other types of toxicity.

These results establish gefitinib plus pemetrexed/carboplatin as an additional first-line option for patients with *EGFR*-mutant NSCLC. The investigators pointed out that this is one of the few regimens that prolongs OS in this setting. The PFS benefit resembled that obtained in the FLAURA trial conducted with the third-generation EGFR TKI osimertinib, although in the present study, patients with PS 2 were included, whereas FLAURA enrolled only patients with PS ≤ 1 [3]. According to the authors, sequencing of effective therapies is important to maximize survival. As osimertinib is active in T790M-mutation–positive tumors, it might be better positioned in the relapsed setting.

## TAK-788 works for exon 20 insertions

Currently approved EGFR TKIs have shown efficacy in lung tumors with

TABLE 1
**Anti-tumor activity of TAK-788 in patients with *EGFR* exon 20 insertions**

| | All patients (n = 28) | Patients with baseline CNS metastases (n = 12) | Patients without baseline CNS metastases (n = 16) |
|---|---|---|---|
| Best response (confirmed), n (%) | | | |
| Partial response | 12 (43) | 3 (25) | 9 (56) |
| Stable disease | 12 (43) | 5 (42) | 7 (44) |
| Progressive disease | 2 (7) | 2 (18) | 0 |
| Not evaluable | 2 (7) | 2 (18) | 0 |
| Confirmed objective response, n (%) [95% CI] | 12 (43) [24-63] | 3 (25) [5-57] | 9 (56) [30-80] |
| Disease control, n (%) [95% CI] | 24 (86) [67-96] | 8 (67) [35-90] | 16 (100) [79-100] |
| Median progression-free survival, months [95% CI] | 7.3 [4.4-not reached] | 3.7 [1.8-not reached] | 8.1 [5.6-not reached] |

common activating *EGFR* mutations including exon 19 deletion and exon 21 L858R mutation but are largely ineffective in patients with *EGFR* exon 20 insertions. Targeted options for patients with these aberrations, which occur in approximately 6 % of cases, are lacking [4]. The experimental EGFR TKI TAK-788 was shown to potently inhibit exon 20 mutations with selectivity over wild-type *EGFR*. TAK-788 is being evaluated in a phase II trial testing 160 mg/d in 7 patient cohorts with NSCLC and other tumor types. At ASCO 2019, Jänne et al. reported the findings for cohort 1 that had refractory, exon-20–positive lung cancer and either active or measurable CNS metastases (but not both) [5]. One or more prior regimens of systemic therapy were required for inclusion; prior TKI therapy was allowed if there had been no response. The efficacy population comprised 28 patients. Median time on treatment was 7.9 months, and 50 % remained on study at the time of the analysis.

TAK-788 160 mg/d demonstrated anti-tumor activity, with a confirmed ORR of 43 % **(Table 1)**. Patients with baseline CNS metastases responded in 25 %, while those without had a response rate of 56 %. In the total population, DCR and PFS amounted to 86 % and 7.3 months, respectively. Responses occurred in patients with various exon 20 insertion variants, including 769_ASV and 773_NPH. AEs proved manageable and consistent with those of other EGFR TKIs, with diarrhea, nausea, and rash being reported as the most common toxicities. Most of the treatment-related AEs were grade 1 and 2 and reversible. In the group of patients treated with at least one dose of TAK-788 160 mg/d during dose escalation or expansion in cohorts 1 to 7 (n = 72), treatment-related grade ≥ 3 AEs emerged in 40 %, and dose reductions became necessary in 25 %. In 14 %, treatment had to be discontinued due to toxicity.

The global EXCLAIM Extension Cohort is further investigating TAK-788 160 mg/d until progression in 91 patients with locally advanced or metastatic NSCLC harboring *EGFR* exon 20 insertions who have received 1 to 2 prior chemotherapies. Treated CNS metastases are allowed in this population. Confirmed ORR per independent review committee constitutes the primary endpoint.

## Real-world experience with afatinib

Observational real-world data obtained in 88 Chinese patients confirmed the efficacy and tolerability of first-line treatment with the second-generation EGFR TKI afatinib [6]. ORR and DCR were 54.5 % and 92.0 %, respectively, and median PFS was 14.2 months. The activity of afatinib was not affected by the presence of brain metastases, dosage or treatment line. Among patients who progressed on afatinib, 65.4 % harbored the T790M mutation. Most of these received third-generation EGFR TKI treatment. Twenty-seven patients continued afatinib treatment beyond tumor progression; this strategy delayed the progression of disease symptoms. Median time to progression of clinical symptoms was 16.3 months.

A retrospective real-world study including 45 patients treated with first-line afatinib at several Spanish hospitals revealed an ORR of 68.9 %, with CR and PR rates of 13.3 % and 55.6 %, respectively [7]. Stable disease occurred in 17.8 %. Median PFS was 27 months, thus exceeding results obtained in clinical trials, and OS had not been reached yet. The authors surmised that the favorable PFS outcomes might be due to a large proportion of patients harboring tumors with exon 19 deletions that respond particularly well to afatinib.

The same cohort of patients was analyzed for the activity of afatinib in advanced age groups [8]. Median age was 71.2 years, with 24 patients (53.3 %) being ≥ 70 years old. Of course, compared to younger patients, the elderly required treatment interruptions and dose adjustments more frequently, but this did not appear to impair safety or efficacy. Afatinib doses were reduced in 47.6% of patients < 70 years and in 75 % of those aged ≥ 70. Treatment discontinuations due to AEs became necessary in 14.3 % vs. 20.8 %. ORRs obtained with afatinib were 76 % and 62.5 %, respectively, and disease control occurred in 90.3 % vs. 83.3 %. Median PFS was 20 months in the younger group but had not been reached in elderly patients yet.

## Clinical implications of certain mutations

A Taiwanese analysis retrospectively evaluated the outcomes of 269 patients with *EGFR*-mutant NSCLC and brain metastases [9]. *EGFR* mutations were categorized into exon 19 deletions, L858R mutations, and uncommon mutations. The results suggested mutation-related differences regarding the natural history of disease and prognosis in patients with brain metastases, with uncommon mutations conferring poorer outcomes. Median PFS for patients with exon 19 deletions, L858R mutations and uncommon mutations was 10.4, 10.0, and 3.2 months, respectively (p = 0.03). For OS, this was 18.1, 17.4, and 12.5

months, respectively (p = 0.05). Compared to gefitinib, treatment with afatinib proved to be a favorable prognostic factor regarding both PFS (HR, 0.57; p = 0.03) and OS (HR, 0.48; p = 0.03).

Clinical features and progression patterns according to the presence of the *EGFR* T790M resistance mutation were the objective of an observational study conducted in Italy [10]. The cohort included 219 patients with *EGFR*-mutant NSCLC who progressed after first-line treatment with gefitinib, erlotinib, or afatinib. Forty-nine percent of patients acquired the T790M mutation. The emergence of T790M was shown to correlate with age < 65 years (p = 0.05) and the presence of exon 19 deletions (p = 0.04). This association was confirmed by a multivariate analysis (p = 0.010 and p = 0.006, respectively). At the time of progression, the T790M-positive group more commonly showed new progression sites (p = 0.005) as well as liver metastases (p < 0.001). The multivariate analysis confirmed the statistical significance of this observation (p = 0.01 and p = 0.008, respectively). Both univariate and multivariate analyses revealed longer median OS in T790M-positive patients (53 vs. 22 months according to univariate analysis; p < 0.0001).

TABLE 2
**Outcomes with osimertinib and comparator TKI treatment (erlotinib, gefitinib) in patients who achieved clearance of plasma *EGFR* mutations at 3 and 6 weeks in the FLAURA trial**

| | | |
|---|---|---|
| **Clearance of plasma *EGFR* mutations at week 3** | | |
| | Osimertinib (n = 106) | Comparator EGFR TKI (n = 102) |
| Events, n (maturity, %) | 50 (47) | 78 (76) |
| Median PFS, months (95 %) | 19.8 (15.1, not calculable) | 10.8 (9.7, 11.1) |
| HR (95 % CI); p value | 0.41 (0.3, 0.6) p < 0.0001 | |
| ORR, % (95 % CI) | 86 (77.7, 91.9) | 88 (80.4, 93.8) |
| Odds ratio (95 % CI) p value | 0.8 (0.4, 1.8) p = 0.6083 | |
| **Clearance of plasma *EGFR* mutations at week 6** | | |
| | Osimertinib (n = 134) | Comparator EGFR TKI (n = 124) |
| Events, n (maturity, %) | 66 (49) | 99 (80) |
| Median PFS, months (95 %) | 19.8 (15.1, not calculable) | 10.2 (9.5, 11.1) |
| HR (95 % CI); p value | 0.40 (0.3, 0.6) p < 0.0001 | |
| ORR, % (95 % CI) | 86 (78.8, 91.2) | 90 (83.7, 94.9) |
| Odds ratio (95 % CI) p value | 0.7 (0.3, 1.4) p = 0.2643 | |

## Early ctDNA clearance: first-line osimertinib …

In the double-blind, randomized, phase III FLAURA trial, first-line treatment with osimertinib resulted in superior PFS compared to EGFR TKI therapy with erlotinib or gefitinib in patients with *EGFR*-positive, advanced NSCLC [3]. Early clearance of circulating tumor DNA (ctDNA) was found to correlate with PFS improvement in the AURA trials [11, 12]. Zhou et al. presented an exploratory analysis of the clinical outcomes associated with the detection of *EGFR* mutations at 3 or 6 weeks after the start of treatment in FLAURA to determine if early ctDNA clearance predicts PFS and ORR [13]. Evaluable ctDNA results at baseline and at weeks 3 and/or 6 were available for 244 and 245 patients in the osimertinib and comparator arms, respectively.

Indeed, the early clearance of plasma *EGFR* mutations appeared to be a prognostic factor for improved outcome. PFS was significantly prolonged in patients who showed clearance of their *EGFR* mutations compared to those who did not both at week 3 (13.5 vs. 9.5 months; HR, 0.57; p < 0.0001) and 6 (13.5 vs. 8.2 months; HR, 0.51; p < 0.0001). Within the group of patients who experienced *EGFR* mutation clearance, those receiv-

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ing osimertinib showed significantly longer PFS both at week 3 (19.8 vs. 10.8 months; HR, 0.41; p < 0.0001) and 6 (19.8 vs. 10.2 months; HR, 0.40; p < 0.0001; **Table 2**). Likewise, if no clearance was achieved at 3 weeks, osimertinib-treated patients fared significantly better regarding PFS than those treated with first-generation EGFR TKIs (11.3 vs. 7.0 months; HR, 0.50; p = 0.001). At 6 weeks, the analysis revealed a trend in favor of osimertinib. Before the start of treatment, persisting *EGFR* mutations indicated worse outcomes, with median PFS of 11.1 *versus* 19.1 months in those who had obtained clearance. ORRs were generally similar across arms without any statistical significances, ranging from 73 % to 90 %.

Overall, these data suggest that patients at increased risk of rapid progression or death on first-line osimertinib treatment could be identified early on. A series analysis of additional timepoints over the course of treatment is underway. Further analyses are investigating the mechanism underlying the high risk of early progression in patients with detectable *EGFR* mutations following EGFR TKI therapy.

### … and later-line osimertinib

Similarly, Song et al. showed that ctDNA clearance within 50 days of the initiation of osimertinib treatment in the pretreated setting can serve as a predictive and prognostic marker [14]. The researchers assessed ctDNA over time in 52 patients with T790M-positive advanced NSCLC from the ASTRIS study who had progressed on EGFR TKI treatment. According to the analysis, patients with undetectable ctDNA at first follow-up within 50 days from the initiation of osimertinib therapy had significantly longer PFS and OS than those with detectable ctDNA (PFS, p = 0.022; OS, p = 0.009).

Moreover, the findings revealed the potential of ctDNA in the early detection of disease progression. Molecular progression occurred in 34 % of patients ahead of radiological progression, with an average lead time of 2.5 months. These patients were more likely to harbor copy number amplifications (CNAs) and *TP53* mutations at the time of radiological progression, with the presence of CNAs indicating shortened PFS and OS compared to those without. Assessment of ctDNA clearance at first follow-up might be commendable considering these insights. ■

## Trial updates and new biomarkers in the field of immunotherapy

### Long-term findings with pembrolizumab: KEYNOTE-001

KEYNOTE-001 was the first trial to demonstrate the activity of the PD-1 inhibitor pembrolizumab in patients with treatment-naïve or previously treated advanced NSCLC [1]. Notably, in this multicohort phase IB study, pembrolizumab showed greater activity with increasing PD-L1 tumor proportion score (TPS). Between May 2012 and July 2014, 550 patients with advanced NSCLC had been enrolled across 4 non-randomized and 2 randomized cohorts. Among these, 101 were treatment-naïve, while 449 had received previous treatment. The 5-year efficacy and safety outcomes of KEYNOTE-001 were reported by Garon et al. at ASCO 2019 [2]. At data cutoff, 100 patients were alive. The recent analysis represents the longest follow-up to date of pembrolizumab treatment in the setting of advanced NSCLC.

In patients with treatment-naïve NSCLC, 23.2 % were alive at 5 years; in the pretreated cohort, this applied to 15.5 %. The authors noted that compared to this, the 5-year OS rate obtained in the United States using standard-of-care cytotoxic chemotherapies between 2008 and 2014 was 5.5 % [3]. In patients with PD-L1 TPS ≥ 50 %, the 5-year OS rates were 29.6 % and 25.0 % for the treatment-naïve and pretreated setting, respectively. Patients with TPS 1 % to 49 % showed lower 5-year survival rates (15.7 % and 12.6 %, respectively). ORRs in the total group amounted to 41.6 % and 22.9 % for treatment-naïve and pretreated patients, respectively, and DCRs were 83.2 % and 58.6 %. Forty-six out of 60 patients who received pembrolizumab treatment for ≥ 2 years were alive at data cutoff. Estimated 5-year OS rates in these 60 patients were 78.6 % and 75.8 % for the treatment-naïve and pretreated cohorts (n = 14 and 46, respectively). Objective responses occurred in 86 % and 91 %, respectively, with a median duration of response of 52.0 months and not reached, respectively.

Updated safety data were consistent with the known profile of pembrolizumab. There was no evidence of cumulative immune-mediated toxicity or late-onset grade 3 to 5 toxicity. Overall, these data continue to demonstrate the potential of pembrolizumab treatment with respect to the improvement of long-term outcomes for treatment-naïve and pretreated patients with advanced NSCLC.

### KEYNOTE-189: updated results & PFS2

The randomized, double-blind, phase III KEYNOTE-189 trial demonstrated the superiority of first-line pembrolizumab combined with a pemetrexed/platinum doublet compared to placebo plus pemetrexed/platinum in metastatic non-squamous NSCLC [4]. Benefits were obtained concerning OS, PFS and ORR; at the same time, the safety profile proved manageable. Gadgeel et al. presented updated efficacy findings

TABLE
**Superiority of pembrolizumab plus pemetrexed/platinum compared to chemotherapy alone irrespective of PD-L1 expression in KEYNOTE-189**

| Endpoint | Total n = 616 | TPS ≥ 50 % n = 202 | TPS ≥ 1-49 % n = 186 | TPS < 1 % n = 190 |
|---|---|---|---|---|
| OS, HR (95 % CI) | 0.56 (0.45-0.70) | 0.59 (0.39-0.88) | 0.62 (0.42-0.92) | 0.52 (0.36-0.74) |
| PFS, HR (95 % CI) | 0.48 (0.40-0.58) | 0.36 (0.26-0.51) | 0.51 (0.36-0.73) | 0.64 (0.47-0.89) |
| ORR, pembro/chemo vs. placebo/chemo | 48.0 % vs. 19.4 % | 62.1 % vs. 24.3 % | 49.2 % vs. 20.7 % | 32.3 % vs. 14.3 % |
| PFS2, HR (95 % CI) | 0.49 (0.40-0.59) | 0.47 (0.33-0.69) | 0.59 (0.41-0.86) | 0.46 (0.33-0.66) |

based on longer follow-up and, for the first time, 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 [5]. PFS2 can be used to quantify the impact of crossover on OS assessment and to determine whether treatment in one line positively or negatively affects the activity of the next line of therapy.

In the ITT population, 410 patients received the pembrolizumab-based combination, whereas 206 were treated with placebo plus chemotherapy. At least one subsequent treatment had been administered in 44.6 % and 59.2 % of patients, respectively. Thirteen percent vs. 54 % had received ≥ 1 subsequent PD-1 or PD-L1 inhibitor. An in-study crossover took place for 40.8 % of patients treated in the control arm.

Pembrolizumab plus pemetrexed and platinum continued to elicit a substantial survival benefit (median OS, 22.0 vs. 10.7 months; HR, 0.56). The 24-month OS rates were 45.5 % vs. 29.9 % for the two arms. Likewise, PFS was approximately doubled (9.0 vs. 4.9 months; HR, 0.48), with 24-month PFS rates of 20.5 % vs. 1.5 %. Moreover, the analysis revealed a substantial benefit of the pembrolizumab-based regimen with regard to PFS2 (17.0 vs. 9.0 months; HR, 0.49). ORRs were also higher in the experimental arm (48.0 % vs. 19.4 %). Benefits of the addition of pembrolizumab were observed for all of these endpoints despite the high rates of patients receiving subsequent therapies and performing in-study cross over, and regardless of PD-L1 expression **(Table)**. After the prolonged follow-up, safety and tolerability of the pembrolizumab-based regimen remained manageable. According to the authors' conclusion, these data confirm that pembrolizumab should be given as part of first-line therapy to maximize outcomes in patients with both PD-L1–expressing and PD-L1-non–expressing metastatic non-squamous NSCLC.

## Significance of absolute PD-L1 levels

Predictive biomarkers for the optimal patient selection for immune checkpoint inhibitor treatment are still lacking, with PD-L1 expression remaining the main clinically applicable test. As part of a multicenter, retrospective study, Aguilar et al. analyzed patients with stage IV NSCLC and PD-L1 TPS of ≥ 50 % to answer the question of whether certain subsets within this range are more likely to benefit from PD-1 inhibitor treatment [6]. The entire cohort comprised 172 patients who received first-line pembrolizumab. Clinicopathological characteristics and clinical outcomes were compared among patients with PD-L1 TPS of 50 % to 74 % (n = 68) vs. 75 % to 100 % (n = 104), and 50 % to 89 % (n = 99) vs. 90 % to 100 % (n = 73).

Indeed, the findings demonstrated that higher PD-L1 TPS levels of ≥ 75 % and ≥ 90 % are associated with improved clinical outcomes. After adjustment for never smokers, squamous histology and mutation status, these patients were shown to derive greater survival benefit than their counterparts with lower PD-L1 expression levels (HRs, 0.63 and 0.50, respectively). The comparisons also yielded significant PFS prolongation for both PD-L1 75 % to 100 % vs. 50 % to 74 % (HR, 0.61) and 90 % to 100 % vs. 50 % to 89 % (HR, 0.52). Similarly, ORRs were in favor of the populations with higher PD-L1 expression. Responders had higher PD-L1 TPS than non-responders. The mean TPS in patients achieving partial or complete response was 82.1 %; in those who showed stable and progressive disease, this was 73.7 % (p = 0.001). The investigators noted that these results should be taken into consideration when deciding between first-line pembrolizumab monotherapy and pembrolizumab plus platinum-doublet chemotherapy. Also, they deserve attention in the context of the design and interpretation of clinical trials for NSCLC with PD-L1 TPS ≥ 50 %.

## Additional markers: *STK11* and *KEAP1*

*STK11*/*LKB1* genomic alterations have been found to be a mediator of "cold" tumor immune microenvironment and a major driver of primary resistance to PD-1 inhibition in non-squamous NSCLC [7]. *STK11* is one of the most frequently inactivated tumor suppressor genes in this disease. It codes for the protein LBK1 that has a role in the regulation of cellular growth and metabolism. Moreover, the *KEAP1* gene is genetically and functionally linked to *STK11*, and the two genes are frequently co-mutated [8, 9].

The retrospective, international study conducted by Skoulidis et al. addressed the effect of these markers as molecular determinants of clinical outcomes obtained with pembrolizumab plus pemetrexed and platinum in the first-line setting of metastatic non-squamous NSCLC [10]. *STK11* and *KEAP1* genomic alterations were shown to be significantly associated with poor outcomes with chemoimmunotherapy. This applied to each of the alterations but particularly to the co-mutated setting. Median PFS was 8.4 months for the double wild-type population, but only 2.7 months for those with double mutants (p < 0.0001); for median OS, this was 20.4 vs. 6.6 months (p = 0.005).

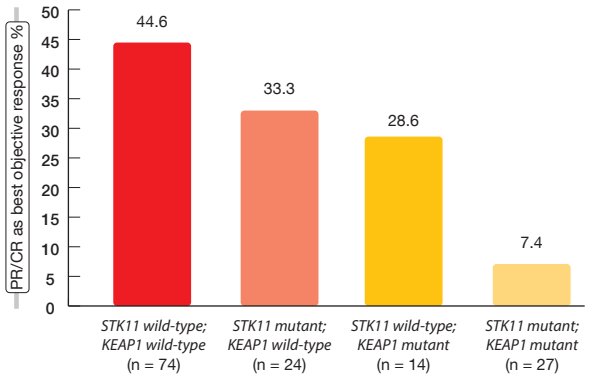


**Figure 1:** : Objective response rates obtained with pembrolizumab plus chemotherapy in *STK11*- and *KEAP1*-defined subgroups

Likewise, ORRs showed gradual worsening when viewed as a function of an increasing number of mutations **(Figure 1)**. In the group of patients with primary refractory disease, as many as 76.5 % had *STK11* and/or *KEAP1* alterations. Also, the presence of these mutations correlated with a lack of apparent PFS or OS benefit from the addition of pembrolizumab to pemetrexed plus platinum. The negative impact of *STK11* and *KEAP1* alterations on clinical outcomes with chemoimmunotherapy was most prominent in patients with high tumor mutational burden and PD-L1–positive tumors. At the same time, in patients with *STK11*- and/or *KEAP1*-mutant tumors, tumor mutational burden and PD-L1 expression did not affect the outcomes.

Based on these findings, the authors proposed the integration of *STK11* and *KEAP1* mutations into a composite genomic marker of poor clinical outcome with chemoimmunotherapy. This would capture a subgroup of approximately 25 % of NSCLC patients with an unmet need for novel strategies to establish effective anti-tumor immunity.

## NLR, PLR, and LDH

Russo et al. demonstrated that easily determinable parameters including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lactate dehydrogenase (LDH) might contribute to patient selection for immunotherapy [11]. The investigators assessed dynamic changes of these inflammation markers over time and the outcomes in 71 consecutive NSCLC patients treated with nivolumab or pembrolizumab. NLR ≥ 5, PLR ≥ 200, and LDH levels ≥ upper normal limit (UNL) were considered high.

Indeed, NLR ≥ 5 was associated with lower PFS and OS, with increasing predictive value from baseline to week 12. PLR ≥ 200 at baseline and week 12 significantly correlated with shorter OS but not PFS. For LDH levels ≥ UNL at baseline, the analysis showed an association with shorter PFS and OS; reductions in LDH levels at 12 weeks compared with baseline values conferred OS improvement. The researchers summarized that baseline levels for NLR, PLR and LDH as well as dynamic changes of LDH levels at 12 weeks significantly predict outcomes in patients treated with single-agent immune checkpoint inhibitors.

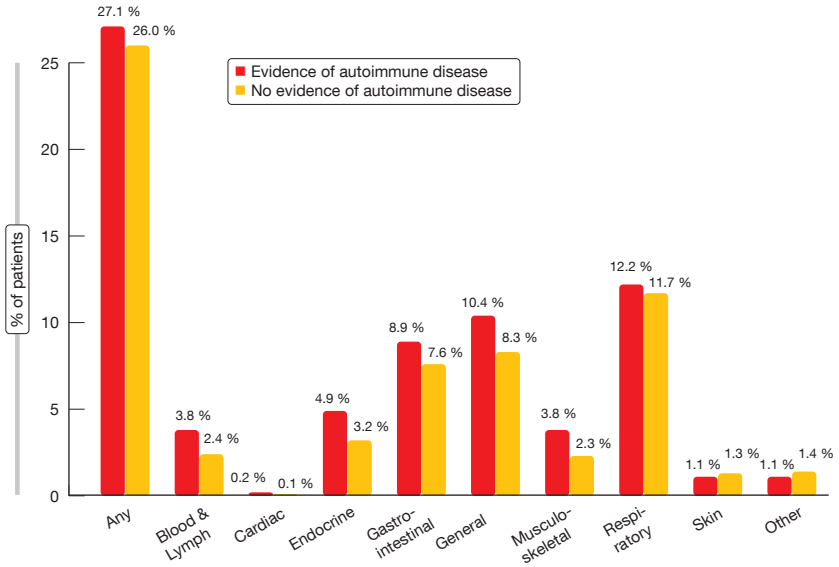


**Figure 2:** Incidence of immune-related AEs in immune-checkpoint-inhibitor–treated patients with and without a history of autoimmune disease

## Does autoimmune disease preclude treatment?

Patients with a history of autoimmune disease are usually excluded from clinical trials testing immunotherapeutic approaches. However, anecdotal and early evidence suggests that immune checkpoint inhibitors are being used in routine care for the treatment of advanced NSCLC even in such patients [12]. Based on these observations, a retrospective observational cohort study was conducted to describe the real-world characteristics and outcomes including AEs in patients with advanced NSCLC with and without a prior history of autoimmune disease who had received at least one dose of an approved immune checkpoint inhibitor in 49 predominantly community-based oncology practices in the USA [13]. Local treatment including surgery and chemoradiation in stage III disease within one year prior to the initiation of immunotherapy represented an exclusion criterion. The records of 2,402 patients were included in the analysis. Twenty-two percent of these (n = 531) had a history of autoimmune disease. Compared to the cohort without a history of autoimmune disease, they showed similar patient and disease characteristics except for a higher proportion of females (54.6 % vs. 43.5 %).

The investigators noted that patients with a history of autoimmune disease had similar efficacy outcomes compared to those without. For OS, real-world PFS, time to treatment discontinuation and time to next treatment, the

  

Kaplan-Meier curves were superimposable, and statistics did not yield any significant differences. With respect to tolerability, patients with a history of autoimmune disease demonstrated an increased incidence of immune-related AEs. This was especially true for endocrine, gastrointestinal, blood and lymphatic disorders, as well as general disorders **(Figure 2)**. Further research is needed to improve understanding of the impact of autoimmune disease on the incidence of immune-related AEs and patient outcomes. ■

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# Blood-based testing in *ALK*-positive disease

**What can we expect from circulating free DNA (cfDNA) as a biomarker in the setting of lung cancer diagnosis and treatment today?**
Blood-based diagnostics can be used in the field of diagnosis of lung cancer, but also for the evaluation of predictive molecular alterations. Today, lung cancer is divided into many small subsets of patients according to individual aberrations in their DNA. With modern technologies, we can diagnose these alterations not only in tissue, but also in the patient's blood. It is extremely interesting to see that the diagnostic accuracy of blood-based tests is improving and can be as high as 80 % or even 90 %. These tests can be used for the initial diagnosis and the selection of the targeted agent, including immunotherapies, and potentially also for treatment monitoring. While tests of circulating free DNA (cfDNA) allow for a general assessment of the presence of DNA in the plasma,

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circulating tumor DNA (ctDNA) focuses on specific alterations with the possibility of establishing allele frequency and quantifying them. At the ASCO Congress, many presentations focused on both cfDNA and ctDNA in patients treated with targeted therapies or immunotherapy, also for diagnostic purposes including screening for the presence of lung cancer, which is becoming a reality.

**Where do you see the clinical significance of cfDNA in *ALK*-positive tumors?**
*ALK*-positive NSCLC represents 5 % of lung adenocarcinomas. This is a clinically important subset of patients, as they can be treated with ALK inhibitors and enjoy unprecedented survival of several years or more. *ALK* rearrangements can be diagnosed not only in the tissue, but also in the plasma, again with diagnostic accuracy of approximately 80 %. Moreover, it is possible to detect variants of *ALK* translocations and quantify the amount of circulating *ALK* in the blood. This has been shown to correlate with response. Decreases in the *ALK* allele frequency in the course of treatment usually tell us that the treat-

ment will be effective. As for other markers, diagnosis and monitoring for treatment efficacy in clinical trials investigating ALK inhibitors can be based on blood testing.

**What are the results of the analysis you presented at this year's ASCO Congress?**

This year I had the pleasure of representing the ALEX investigators who contributed to the enrollment of patients with *ALK*-positive NSCLC [1]. Patients were randomized to first-line therapy with either crizotinib, which used to be the standard of care, or the novel ALK inhibitor alectinib. PFS, OS and other endpoints were assessed. The analysis we presented investigated circulating free tumor DNA as a proxy of tumor burden and correlated that with patient prognosis. We showed that cfDNA correlates with tumor burden; patients with a high number of metastases or huge tumors had higher cfDNA levels and worse prognosis with both crizotinib and alectinib, although alectinib-treated patients did better independent of their cfDNA levels. Therefore, cfDNA probably explains why PFS and OS differ across patients. In addition, it should be noted that cfDNA testing is quite a simple measurement. Out of 300 ALEX patients, the data for over 270 individuals were available for the statistical analysis.

At present, these results only have prognostic implications. The underlying tumor burden that is quantified using a simple test can provide information on which patient will do well and which patient has a higher likelihood of failing on ALK-targeted treatment.

In the future, however, we would also like to evaluate the temporal changes in cfDNA and investigate associations with radiologic relapse. Also, cfDNA tests might be used as predictive assays to identify patients who do not initially respond to ALK inhibitor therapy. This remains to be explored. ■

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# Rare mutations: taking treatment one step further

## GEOMETRY mono-1: capmatinib in *MET*-dysregulated NSCLC

*MET* exon 14 skipping mutations (*MET*ex14) have been reported in 3 % to 4 % of NSCLC patients [1-3]. They confer poor prognosis and poor responses to standard therapies including immunotherapy [4-8]. Moreover, patients with *MET* alterations are generally older, which implies that tolerable strategies are called for. Capmatinib has been developed as a highly selective, potent MET inhibitor with *in vitro* and *in vivo* activity against preclinical cancer models harboring *MET* activation [9].

The multicohort, multicenter, phase II GEOMETRY mono-1 trial investigated capmatinib 400 mg twice daily in patients with stage IIIB/IV NSCLC and *MET*ex14. Preliminary efficacy data presented at ESMO 2018 have shown deep responses irrespective of the line of treatment, as well as CNS activity [10]. At the ASCO 2019 Congress, Wolf et al. reported the primary efficacy analysis and other analyses for Cohorts 4 and 5b [11]. Cohort 4 evaluated capmatinib in the second and third line (n = 69), while Cohort 5b included treatment-naïve patients (n = 28). In the pretreated cohort, 74 % had received one treatment line; here, platinum-based chemotherapy had been administered in 88.4 %. Most of the patients in both cohorts showed concurrent *MET* amplification. The two cohorts were analyzed separately and had independent, prospectively designed statistical hypotheses. ORR according to the blinded independent review committee (BIRC) constituted the primary endpoint.

## Extra- and intracranial effects

In Cohort 4, ORR by BIRC amounted to 40.6 %, while DCR, as the key secondary endpoint, was 78.3 % **(Table 1)**. For Cohort 5b, ORR and DCR were 67.9 % and 96.4 %, respectively. Rapid, deep and durable responses occurred across both cohorts. Median duration of response was 9.72 and 11.14 months in Cohorts 4 and 5b, respectively. At 12 months, 25.8 % and 49.7 % of patients, respectively, remained progression-free; median PFS was 5.42 and 9.69 months. All of these outcomes were consistent between BIRC and investigator assessment. The neuro-radiologist review confirmed activity of the capmatinib treatment against brain metastases. Seven of 13 evaluable patients who had CNS lesions at baseline achieved intracranial responses, with four patients even experiencing complete resolution of all metastases. Twelve patients obtained intracranial disease control. Intracranial responses were demonstrated to develop as rapidly as those observed outside of the CNS.

Furthermore, the investigators found that deep and lasting responses occurred independently of the type of *MET* mutation leading to *MET*ex14 or co-occurrence of *MET* amplification. Both next generation sequencing and reverse transcriptase polymerase chain reaction demonstrated high sensitivity for the detection of *MET*ex14 in tumor tissue, with a concordance rate of 99 %. As is the case for other molecular drivers, tumor mutational burden was low in these patients (median, < 6 mut/MB in tumor tissue) compared to those with wild-type NSCLC, and similar across treatment lines.

The safety analysis dataset represents the largest dataset of *MET*-dysregulated NSCLC patients up to now

  

(n = 334). Capmatinib showed high tolerability, with few grade-3/4 events. Peripheral edema, nausea, and increased creatinine levels were the most frequently reported AEs. Dose adjustments and treatment discontinuation due to treatment-related AEs became necessary in 21.9 % and 11.1 %, respectively. In their summary, the authors pointed out that the favorable ORR in the treatment-naïve cohort highlights the importance of early molecular testing. Capmatinib appears to be a new treatment option in the rare but challenging population of patients with advanced NSCLC and *MET* dysregulation.

## Tepotinib: the VISION study

Another highly selective, potent MET inhibitor is tepotinib, which is being evaluated in the single-arm phase II VISION trial in patients with stage IIIB/IV NSCLC of all histologies and *MET* alterations according to tissue or liquid biopsy. In Cohort A, patients with *MET*ex14 skipping mutations are receiving tepotinib 500 mg/d until progression. Tepotinib is used in the first-, second- and third-line settings. Paik reported interim findings including ORR assessed by independent review (i.e., the primary endpoint) and select secondary outcomes for Cohort A [12]. Eighty-seven patients had been treated at the time of the analysis.

Tepotinib elicited ORRs of 50.0 % and 45.1 % by independent review according to liquid biopsy and tissue biopsy, respectively. Reponses lasted for 12.4 and 15.7 months, respectively. Disease control was achieved in 66.7 % and 72.5 %, respectively. The treatment activity was consistent across treatment lines. This also held true for tumor shrinkage; 92 % of patients according to both independent review and investigator read experienced tumor shrinkage in the first- and second-line settings. In the third line and beyond, evidence of tumor shrinkage was found in ≥ 75 % of cases. Responses occurred early on and were durable across treatment lines. Median duration of response exceeded one year in all analysis subsets and was 14.3 months overall. Patients who showed brain metastases at baseline benefitted equally from treatment. Median PFS was 9.5 and 10.8 months in the total cohort according to liquid biopsy and tissue biopsy, respectively.

TABLE 1
**Response rates achieved with cabmatinib in advanced NSCLC harboring *MET*ex14 mutation**

| | Blinded independent review | Investigator assessment |
|---|---|---|
| | **Cohort 4 (second/third line) n = 69** | |
| Complete response, n (%) | 0 | 1 (1.4) |
| Partial response, n (%) | 28 (40.6) | 28 (40.6) |
| Stable disease, n (%) | 25 (36.2) | 22 (31.9) |
| Non-CR/non-PD, n (%) | 1 (1.4) | 2 (2.9) |
| Progressive disease, n (%) | 6 (8.7) | 7 (10.1) |
| Not evaluable, n (%) | 9 (13.0) | 9 (13.0) |
| Overall response rate, % (95 % CI) | 40.6 (28.9, 53.1) | 42.0 (30.2, 54.5) |
| Disease control rate % (95 % CI) | 78.3 (66.7, 87.3) | 76.8 (65.1, 86.1) |
| | **Cohort 5b (first line) n = 28** | |
| Complete response, n (%) | 1 (3.6) | 0 |
| Partial response, n (%) | 18 (64.3) | 17 (60.7) |
| Stable disease, n (%) | 8 (28.6) | 10 (35.7) |
| Progressive disease, n (%) | 1 (3.6) | 1 (3.6) |
| Overall response rate, % (95 % CI) | 67.9 (47.6, 84.1) | 60.7 (40.6, 78.5) |
| Disease control rate % (95 % CI) | 96.4 (81.7, 99.9) | 96.4 (81.7, 99.9) |

The trial demonstrated a favorable safety profile, with peripheral edema, nausea, and diarrhea reported as the most common AEs. No grade 4 or 5 treatment-related AEs occurred. The investigators concluded that tepotinib shows promising and durable clinical activity in patients with *MET*ex14 mutations. The VISION study is ongoing; results for Cohort B, which includes patients with *MET* amplification in the absence of *MET*ex14 skipping mutations, will be presented in the future.

## BLU-667 for *RET*-positive disease

*RET* alterations are found in approximately 1 % to 2 % of NSCLC cases [13, 14]. There is an unmet medical need in these patients, as no significant benefits from existing strategies such as chemotherapy, immunotherapy or multikinase inhibitor treatment have been observed for them [15-17]. No selective RET inhibitors have been approved to date.

The investigational agent BLU-667, which potently and selectively inhibits *RET* alterations and *RET* resistance mutants [18, 19], might be on the verge of filling this gap. Gainor et al. presented findings from the phase I ARROW study [20]. The dose-escalation part of this trial identified 400 mg/d as the ideal dose. Part 2 is currently enrolling patients into seven expansion cohorts with various *RET*-altered advanced solid tumors. Asymptomatic brain metastases are allowed. Two of the cohorts contain NSCLC patients, with one cohort being platinum-naïve and the other being platinum-pretreated. The latter had received a median of two prior lines of therapy. Forty percent in the overall NSCLC population showed CNS lesions. Known *RET* fusion partners were mainly *KIF5B* (66 %) and *CCDC6* (13 %). ORR and safety constitute the primary objectives of the ARROW study.

## Clinical benefits and RET clearance

According to the preliminary efficacy analysis conducted in 48 NSCLC patients 35 of whom were pretreated, BLU-667 demonstrated broad and durable anti-tumor activity, with ORRs of 58 %

and 60 % in the total cohort and the pretreated group, respectively. DCRs were 96 % and 100 % for these two populations. Most responses emerged already at the time of the first follow-up imaging assessment. At data cutoff, 82 % of responding patients remained on treatment, and the median duration of response had not been reached yet. Including the dose-escalation phase, the patients have been on treatment for up to 24 months. BLU-667 retained activity irrespective of prior immune checkpoint inhibitor treatment, *RET* fusion genotypes, and CNS involvement. Seven out of nine patients who had measurable untreated brain metastases at baseline achieved shrinkage of these lesions **(Figure)**. No patient treated with a starting dose of 400 mg/d experienced progression due to new CNS involvement. Eighteen of 20 patients with detectable *RET* fusion ctDNA at baseline showed complete clearance within the first treatment cycle.

The safety analysis comprised 120 patients, 91 of whom were platinum-pretreated. BLU-667 was well tolerated, with toxicities generally being low-grade, reversible and consistent with the drug's selectivity profile. The most common AEs included constipation, neutropenia, transaminase elevations, fatigue, and hypertension. Among grade ≥ 3 AEs, neutropenia and hypertension prevailed in 13 % each. In total, 7 % of patients discontinued BLU-667 due to treatment-related toxicity. As the authors noted, these data support the expansion of the ARROW trial in treatment-naïve NSCLC patients.

## Convincing larotrectinib activity

Rearrangements involving the *NTRK* genes have been identified across a broad range of malignancies, with an estimated frequency of 1 % in all solid tumors [21]. The first-in-class, highly selective TRK inhibitor larotrectinib demonstrated robust efficacy in an integrated expanded dataset of 109 patients regardless of tumor type or age [22]. Hong et al. evaluated the efficacy and safety of larotrectinib 100 mg twice daily in 83 adult patients with locally advanced or metastatic solid tumors treated in three clinical trials (adult phase I, NCT02122913; SCOUT, NCT02637687; NAVIGATE, NCT02576431) [23]. Patients with a total of 12 tumor types had been included in these studies; 13 % of them had been diagnosed with lung cancer.

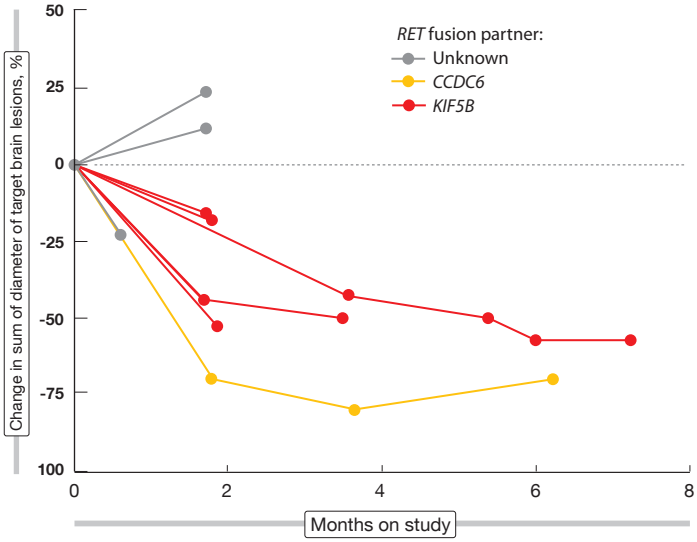


**Figure:** Shrinkage of brain metastases in RET-positive lung cancer patients receiving BLU-667

Larotrectinib was shown to induce strong and durable responses in the entire population. ORR by independent review committee was 68 %. CR, PR and SD were observed in 17 %, 51 %, and 15 %, respectively. Responses occurred irrespective of tumor type. At a median follow-up of 17.5 months, median duration of response had not been reached yet for patients with confirmed responses. Seventy-nine percent of responders were estimated to be in response longer than 12 months. Median PFS was 25.8 months, and median OS had not been reached.

Larotrectinib was well tolerated, with the majority of AEs being graded as 1 or 2. The most common AEs included fatigue (40 %), dizziness (36 %), and nausea (29 %). Overall, these data provide strong evidence in support of testing for *TRK* fusions in adult patients with advanced solid tumors regardless of the site of the primary tumor.

## Characteristics of *NRG1*-positive lung cancer

*NRG1* fusions are found in approximately 1.7 % of patients with adenocarcinoma of the lung [24]. These fusions activate HER3/HER2 signaling, supporting the therapeutic use of HER3 and/or HER2 inhibitors. However, characterization of clinicopathological and molecular features of this disease is lacking, as well as evidence on the efficacy of systemic treatments in a large cohort of patients with *NRG1*-positive NSCLC. Duruisseaux et al. therefore launched a registry involving a global, multicenter network of thoracic oncologists from 17 institutions in eight countries [25]. These identified a total of 117 patients who had confirmed *NRG1*-fusion–positive NSCLC. Clinicopathological/molecular features and clinical outcomes were collected retrospectively.
The cohort contained a high proportion of women (54.7 %) and never smokers (43.6 %). A median of 40 pack years was reported for smokers. The tumors mainly showed adenocarcinoma histology (94.9 %), with the mucinous subtype dominating (71 %). In terms of genetic characteristics, *NRG1* fusions had upstream partner genes in 58.9 % of cases; here, *CD74* and *SCLA3A2* were most common. *NRG1* fusions were mainly identified using RNA-based assays. In patients who had metastatic disease, the lung was the most common organ site of dissemination. Stage-IV *NRG1*-positive NSCLCs showed a remarkably good prognosis, with median OS of 4.83 years. For stages I and III, median OS had not been reached yet, and for stage II, this was 4.4 years.

Data on the efficacy of systemic therapies were available for 23 patients. Platinum-based chemotherapy was administered in 18 cases **(Table 2)**. Here, two patients obtained PR (11 %), and SD occurred in nine individuals (50 %).

TABLE 2
**Systemic treatment administered in 23 patients with *NRG1*-fusion–positive NSCLC in the metastatic setting**

| Type of treatment | n (%) |
|---|---|
| Chemotherapy | 18 (60) |
| Platinum-based | 18 (60) |
| Pemetrexed-based | 14 (47) |
| Anti-PD-1/anti-PD-L1 | |
| Monotherapy | 6 (20) |
| Combined with chemotherapy | 5 (17) |
| Anti-HER2/HER3 | 16 (53) |
| Afatinib | 13 (43) |
| RO5479599 | 2 (7) |
| GSK2849330 | 1 (3) |
| MCLA-128 | 1 (3) |

Among patients treated with afatinib as a single agent or in combination (n = 13, with efficacy data available for 12), one achieved CR (8 %), while three developed PR (25 %) and two SD (17 %). Two patients experienced responses lasting for more than one year. Median PFS with afatinib was 2.0 months, while median OS had not been reached yet. However, OS from the diagnosis of the metastatic stage did not differ across patients with and without afatinib treatment. For single-agent anti-PD-1/L1 therapy, no responses were observed; this also applied to chemoimmunotherapy.

The authors concluded that afatinib treatment might not change the natural history of the metastatic disease, although long-lasting responses occurred with this treatment in a few patients. Novel targeted therapeutic approaches are called for. RNA-based assays might be the test method of choice for the identification of *NRG1* fusions. ■

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# Small-cell tumors: improvements in the second-line setting

## Lurbinectedin monotherapy

Only limited therapeutic options are available for patients with relapsing small-cell lung cancer (SCLC). Topotecan is the only FDA-approved treatment for platinum-sensitive disease in the second-line setting. However, it induces merely modest clinical benefits, while at the same time giving rise to significant hematological toxicity.

A novel approach might result from the inhibition of deregulated oncogenic transcription factors. SCLC has been found to be a transcription-addicted tumor [1]. Rudin et al. described four molecular SCLC subtypes defined by the differential expression of four key transcription regulators [2]. Lurbinectedin, a selective inhibitor of oncogenic transcription, acts by binding DNA [3]. It not only targets tumor cells, inducing apoptosis, but also downregulates IL-6, IL-8, CCL2 and VEGF by inhibiting active transcription in tumor-associated macrophages [4].

A single-arm, phase II basket trial investigated lurbinectedin monotherapy in nine different tumor types. Paz-Ares et at. presented the findings in patients with SCLC, who received lurbinectedin 3.2 mg/m² every 3 weeks after one chemotherapy line [5]. Prior immunotherapy was allowed, whereas CNS involvement was not. A total of 105 patients entered the trial between October 2015 and October 2018 and were treated with a median of 4 cycles. Among these, 60 were defined as platinum-sensitive (i. e., chemotherapy-free interval ≥ 90 days) and 45 as platinum-resistant (chemotherapy-free interval < 90 days).

## Encouraging findings in resistant disease

The antitumor activity of lurbinectedin was substantial, with an ORR of 35.2 % and a DCR of 68.6 %. Responses lasted for a median of 5.3 months. Compared to the platinum-sensitive group, the cohort with resistant disease showed lower ORRs **(Table)**. However, these rates are still notable, which is important in a setting that lacks approved options. Patients with platinum-resistant disease experienced responses in 22.2 % and disease control in 51.1 %. Three of five patients with resistant SCLC and two of three with sensitive tumors in whom prior immunotherapy had failed achieved confirmed responses with lurbinectedin treatment. Duration of response was 4.7 and 6.2 months in the resistant and sensitive cohorts, respectively. Decreases in tumor size occurred in 65 % of the total population.

TABLE
**Activity of lurbinectedin in patients with platinum-resistant and platinum-sensitive SCLC**

| | Platinum-resistant (CTFI < 90 days) n = 45 | Platinum-sensitive (CTFI ≥ 90 days) n = 60 |
|---|---|---|
| ORR, % (95 % CI) | 22.2 (11.2-37.1) | 45.0 (32.1-58.4) |
| Best response (confirmed) | n (%) | n (%) |
| PR | 10 (22.2) | 27 (45.0) |
| SD | 13 (28.9) | 22 (36.7) |
| PD | 18 (40.0) | 10 (16.7) |
| Not evaluable | 4 (8.9) | 1 (1.7) |
| Disease control rate, % (95 % CI) | 51.1 (35.8-66.3) | 81.7 (69.6-90.5) |

CTFI, chemotherapy-free interval

Median PFS was 3.9 months (2.6 and 4.6 months for resistant and sensitive patients, respectively), with a 6-month PFS rate of 33.6 % (18.8 % and 44.6 %, respectively). For OS, the median was 9.3 months in the overall cohort (5.0 and 11.9 months, respectively), and the 12-month survival rate amounted to 34.2 % (15.9 % and 48.3 %, respectively). Lurbinectedin showed a favorable and manageable safety profile. Among the non-hematological AEs, the most frequently reported AEs included fatigue, nausea, decreased appetite and vomiting. Neutropenia occurred as the most common hematological toxicity. The analysis revealed low rates of serious AEs (10.5 %) and AEs leading to treatment discontinuation (1.9 %). As the authors stated based on these observations, lurbinectedin emerges as a potential new treatment alternative for SCLC patients treated in the second line.

## Carfilzomib plus irinotecan

A single-arm, phase II trial stratified by platinum sensitivity evaluated the combination of irinotecan (125 mg/m² on days 1, 8 and 15 of a 28-day cycle) and the proteasome inhibitor carfilzomib in patients with extensive-disease SCLC progressing after one prior platinum-based regimen [6]. During the first cycle, carfilzomib was administered at a dose of 20mg/m² on days 1 and 2, followed by 36 mg/m² on all subsequent days (days 1, 2, 8, 9, 15 and 16 of a 28-day cycle). The rationale for the combined approach was the expected synergy of these drugs, as the inactivation of proteasome function allows for an increase in apoptosis and interference with Topo-I degradation. Overall, 62 patients participated; 25 of these were platinum-refractory (PR stratum), while 37 were platinum-sensitive (PS stratum). OS at 6 months was defined as the primary endpoint.

Irinotecan plus carfilzomib demonstrated effectivity in relapsed SCLC, with 6-month OS rates of 54 % and 59 % in the PR and PS strata, respectively. Median OS amounted to 6.8 and 6.9 months, respectively. Median PFS was 3.3 and 3.6 months, respectively. At 56.0 % and 67.6 %, disease control rates were comparable to those observed with other second-line agents, although CRs and PRs were lower in comparison (1.6 % and 16.1 %, respectively, for the total

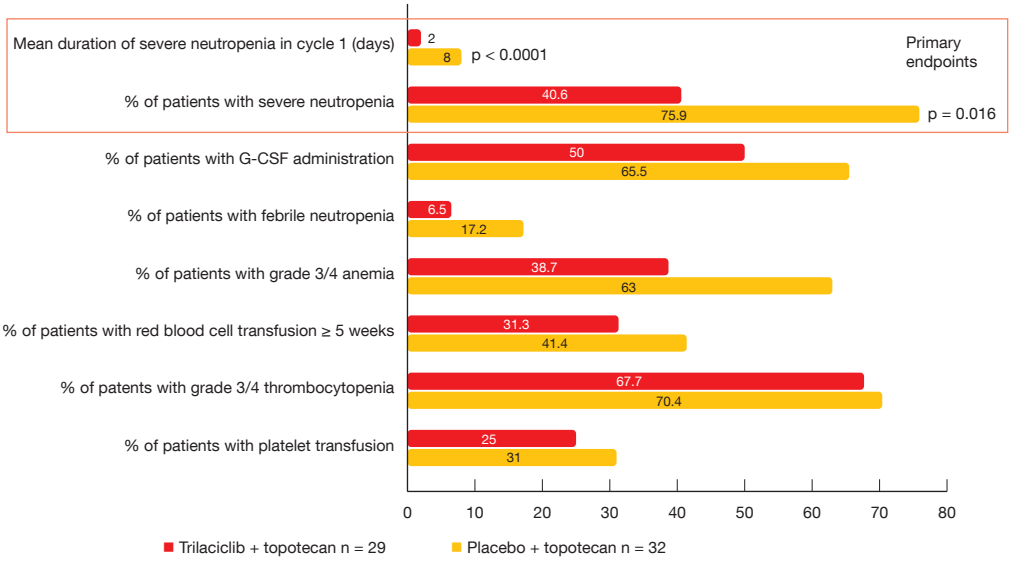


**Figure:** Myelopreservation benefits achieved with the administration of trilaciclib prior to topotecan in the second- or third-line setting

population). Assessments of the chymotrypsin-like activity (CLA) in peripheral blood mononuclear cells, which is a measure of the effect of carfilzomib on proteasome activity, revealed similar CLA declines in both platinum-sensitive and platinum-refractory patients. This suggests that proteasome inhibition did not account for the unanticipated success in the refractory group.

The safety profile of the combination resembled that of single-agent topotecan, amrubicin and irinotecan in relapsed SCLC. Forty-seven percent of patients experienced at least one grade-3 AE. Grade-4 toxicities occurred in 8 patients (12.9 %) and three (4.8 %) died, with two possible fatalities (i. e., myocardial infarction, lung infection) and one probable fatality (i. e., sepsis). According to the conclusion of the scientists, irinotecan plus carfilzomib is a viable option in relapsed SCLC and can be considered after progression on immunotherapy or in patients who cannot receive checkpoint inhibitors. However, due to toxicity, this regimen is not recommended for frail individuals with performance status > 2. The combination should be further explored in a confirmatory phase III trial.

## Myelopreservation with trilaciclib

Despite the availability of rescue medications, there is still a significant unmet medical need in SCLC patients treated with topotecan as this drug causes severe myelosuppression in a significant percentage of cases. Neutropenia occurs in more than half of patients treated with topotecan at full dose, with a febrile neutropenia rate of approximately 3 % [7]. G-CSF rescue is frequently indispensable but often induces bone pain as a side effect [8]. Anemia and thrombocytopenia are observed in 31 % and 54 %, respectively, necessitating the use of erythropoiesis-stimulating agents or transfusions in many patients [7]. At the same time, dose reductions or schedule changes of topotecan have unknown effects on the efficacy of this treatment.

The CDK4/6 inhibitor trilaciclib is a first-in-class, potent, intravenous myelopreservation agent. It transiently blocks progression through the cell cycle, thereby preventing chemotherapy-associated damage in hematopoietic stem and progenitor cells. Dragnev et al. already demonstrated benefits of trilaciclib with respect to multi-lineage myelosuppression in extensive-stage SCLC patients receiving first-line chemotherapy [9]. The randomized, double-blind, placebo-controlled, phase II G1T28-03 study presented at ASCO 2019 tested trilaciclib in patients with extensive-stage SCLC receiving topotecan in the second or third-line setting [10]. In the experimental arm, 32 patients were treated with trilaciclib plus topotecan 1.5 mg/m² until progression, while 29 patients received placebo plus topotecan in the control arm. Trilaciclib was administered intravenously on days 1 to 5 prior to topotecan.

## Benefits without impaired efficacy

Indeed, the administration of trilaciclib made topotecan treatment safer and more tolerable. Compared to the placebo arm, the patients in the experimental arm completed more cycles and had fewer dose reductions. Myelopreservation benefits occurred across multiple lineages, with reductions in cytopenia rates and diminished necessity of rescue treatments **(Figure)**. For the primary endpoints, i. e., mean duration of severe neutropenia in cycle 1 and occurrence of severe neutropenia, the analysis yielded significant differences in favor of the trilaciclib-treated group ($p < 0.0001$ and $p = 0.016$, respectively). Duration of severe neutropenia is a surrogate for an increased risk of febrile neutropenia, infection, intravenous antibiotic use and hospitalization.

Accordingly, the trilaciclib arm experienced fewer high-grade hematological toxicities, particularly neutropenia and anemia, and improved patient experience by decreasing the risk of deterioration during chemotherapy as compared to placebo, according to validated patient-reported outcome instruments. Benefits of trilaciclib were observed for general and physical wellbeing, quality-of-life measures specific for lung cancer

patients, symptoms and impact of fatigue, and symptoms and effects on physical and functional wellbeing due to anemia.

At the same time, the use of trilaciclib did not impair the efficacy of chemotherapy. ORR, PFS and OS were comparable across the trilaciclib and placebo arms. Trilaciclib-related AEs of special interest were primarily low-grade and included headache, infusion-related reactions, and phlebitis. In their conclusion, the authors noted that these data extend the evidence for the clinical benefits of trilaciclib in SCLC as a first-in-class myelopreservation agent for patients treated with topotecan in the second- or third-line setting. ■

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# Expansion of clinical trial enrollment criteria: what would we gain?

## Broadened vs. traditional: retrospective analysis

In 2017, the American Society of Clinical Oncology and the non-profit organization Friends of Cancer Research noted in their joint statement that trial enrollment criteria should strive for inclusiveness to make trial populations more representative and to maximize generalizability of findings [1]. Also, this would enable more patients to participate and accelerate accrual, resulting in expedited availability of new therapies.

Harvey et al. conducted a retrospective study using real-world data obtained between January 2011 and December 2018 to demonstrate the impact of broadened versus traditional criteria on the eligibility of patients with advanced NSCLC [2]. Based on the ASCO CancerLinQ Discovery (CLQD) deidentified electronic health record, patients who received treatment after a diagnosis of advanced NSCLC were identified. Outcome measures related to the number and characteristics of patients eligible by traditional vs. broadened criteria.

Specifically, three domains of criteria were evaluated, i. e., prior and concurrent cancers, brain metastases, and kidney function. Patients with a cancer history, brain metastases and creatinine clearance ≤ 60 mL/min are usually excluded from clinical studies. According to the broadened criteria, all cases with another primary cancer diagnosis were included, as well as all patients with brain metastases irrespective of treatment status and clinical stability, and those with creatinine clearance ≥ 30 mL/min.

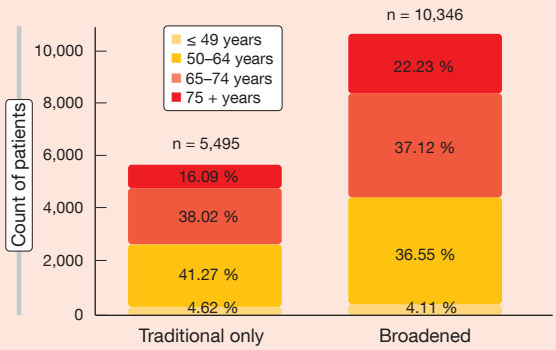


**Figure:** Distribution of age groups in the traditional and broadened cohorts

## Doubling of eligible patients

Within the total group of 10,500 patients, according to the traditional criteria, the proportions of patients excluded due to prior/concurrent cancers, brain metastases, and creatinine clearance ≤ 60 mL/min were 21.5 %, 21.2 %, and 14.4 %, respectively. Overall, 47.7 % of these patients would not have been able to participate in clinical trials. The broadened criteria, on the other hand, only prompted exclusion of 1.5 % based on the creatinine clearance cut-off. Thus, the traditional and broadened cohorts comprised 5,495 and 10,346 patients, respectively, with the broadened cohort containing a comparably higher percentage of patients aged > 75 years (22.23 % vs. 16.09 %; **Figure**).

This analysis shows that the use of expanded criteria would enable almost twice

  

as many patients with advanced NSCLC to consider trial participation. Moreover, these criteria are likely to result in trial participants being more reflective of a broader patient population. The authors noted that narrower criteria should only be used based on a compelling scientific rationale. Additional recommendations by ASCO and Friends of Cancer Research are in progress.

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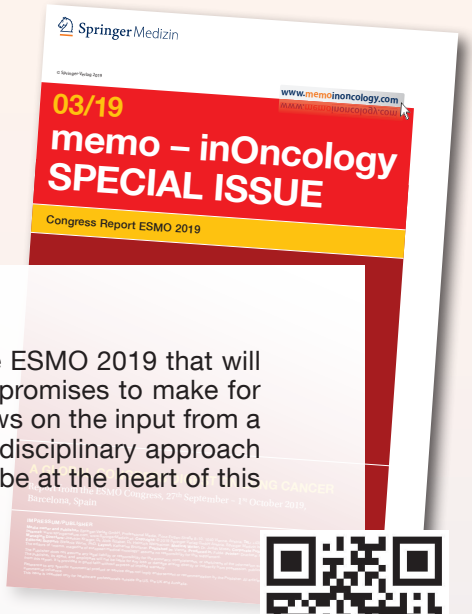


## Forthcoming Special Issue

This special issue will be offering a synopsis from the ESMO 2019 that will be held in Barcelona in September 2019. The report promises to make for stimulating reading, as the ESMO Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

# ESMO 2019
## Annual Meeting
BARCELONA, SPAIN, SEPTEMBER 27 – OCTOBER 1, 2019


For additional expert information on oncology topics, why not explore memo inoncology (**www.memoinoncology.com**), an educational webpage sponsored by Boehringer Ingelheim. Not only will you always find the latest issue of the memo – inoncology Special Issue series here, you will in future also be able to look up previous issues by congress and year. In addition, this webpage aims to offer a number of further educational materials specifically chosen to complement each issue as it is published.

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