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A GLOBAL CONGRESS DIGEST ON LUNG CANCER

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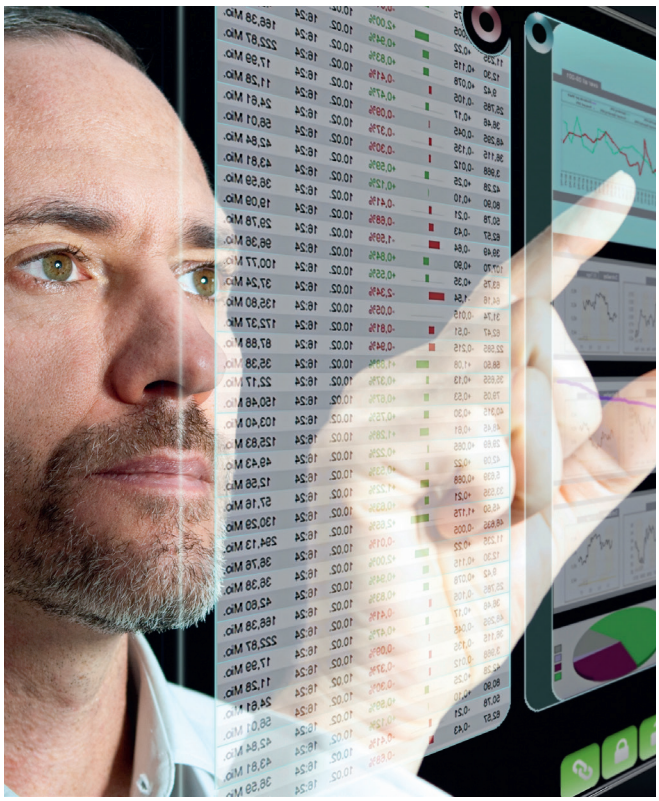

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Preface

Dear Colleagues,

As in 2020, the 2021 Annual Meeting of the American Society of Clinical Oncology (ASCO) was held online, with both the scientific and education programs taking place on June 4-8. Among more than 2,500 abstracts presented, findings in the area of lung cancer made for exiting news. Immune checkpoint inhibition has been moving forward in the continuum of care across the treatment lines and is now defining new standards in early-stage lung cancer. In patients who underwent complete resection, the IMpower010 trial established PD-L1 inhibition as a new adjuvant option in stage II-IIIA, PD-L1–expressing NSCLC. Previously, based on the PACIFIC study, another PD-L1 inhibitor has already transformed the treatment of patients with unresectable stage III tumors responding to chemoradiation. Here, the updated results have revealed lasting benefits.

Important data have also been obtained for targeted therapy that involves not only individualized tailoring of treatment but also the handling of resistance that emerges with it. Various mechanisms of resistance depending on the type of the administered agent have been identified for *EGFR*-mutant lung cancer. The answer can be targeting of alternative aberrations such as *HER3* or the use of regimens that inhibit both likely resistance mechanisms and the primary target. Inactivating somatic mutations such as *STK11* and *KEAP1* can also have a predictive effect regarding the activity of KRAS inhibition from the outset, according to exploratory analyses of the CodeBreaK100 trial. Immunotherapy and targeted treatment may intertwine, which applies particularly to the *KRAS*-mutated setting as demonstrated by various analyses reported at ASCO 2021. Sequencing can play an important role in terms of use of checkpoint inhibitors and targeted tyrosine kinase inhibitors but also antiangiogenic agents, with a view to creating an immunosupportive tumor microenvironment.

Moreover, small-cell lung cancer is being increasingly characterized at the molecular level, with differential expression of genes and biomarkers possibly informing therapeutic vulnerabilities in the future. For the time being, innovative strategies such as bispecific T-cell engager therapies are tested in patients with relapsed SCLC who have a high unmet medical need. While the armamentarium is being refined to improve efficacy and tolerability at the individual patient level, we hope to meet again at future conferences to hear about breakthroughs that will further advance daily patient care.

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Early-stage lung cancer: immunotherapeutic standards

IMpower010: adjuvant administration of atezolizumab

Despite established strategies such as platinum-based chemotherapy and EGFR-targeted agents, there is a high unmet need for improved adjuvant treatment in the setting of completely resected early-stage NSCLC (stage IB-IIIA). Therefore, the global phase III IMpower010 trial tested the anti-PD-L1 antibody atezolizumab 1,200 mg every 21 days for 16 cycles compared to best supportive care (BSC) in patients with stage IB-IIIA lung cancer who had undergone lobectomy or pneumonectomy followed by 1-4 cycles of chemotherapy. *EGFR* mutations and *ALK* rearrangements did not represent exclusion criteria in this study. Disease-free survival (DFS) was defined as the primary endpoint. This was tested hierarchically in three primary analysis populations: the PD-L1 tumor cell (TC) ≥ 1 % stage II-IIIA population (n = 476); the all-randomized stage II-IIIA population (n = 882); and the ITT population (stage IB-IIIA; n = 1,005).

According to the pre-planned interim analysis presented by Wakelee et al. at the ASCO 2021 Annual Meeting, atezolizumab gave rise to a significant DFS benefit in both the PD-L1 TC ≥ 1 % stage II-IIIA population (not reached vs. 35.3 months; HR, 0.66; p = 0.004; **Figure 1**) and the all-randomized stage II-IIIA population (42.3 vs. 35.3 months; HR, 0.79; p = 0.02) [1]. The curves separated early and remained separated in both populations. Subgroup analyses of the all-randomized cohort indicated that the DFS benefit increased with PD-L1 expression, as risk reductions for the groups with PD-L1 TC ≥ 50 %, ≥ 1, and < 1 % were 57 %, 34 % and 3 %, respectively. In the ITT population including patients with stage IB disease, DFS did not cross the significance boundary at

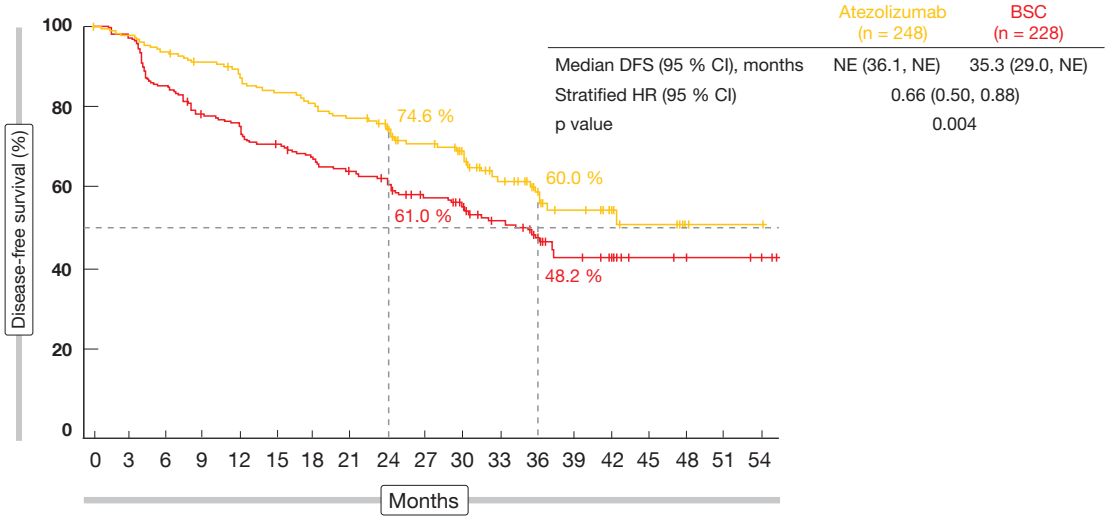

Figure 1: Superiority of atezolizumab vs. BSC for disease-free survival in the PD-L1 tumor cell ≥ 1 % stage II-IIIA population

the time of the analysis (not reached vs. 37.2 months; HR, 0.81). Testing will continue in this group.

Overall survival (OS) data were immature and not formally assessed according to the statistical plan. However, a trend towards OS improvement emerged in the PD-L1 ≥ 1 % stage II-IIIA population (HR, 0.77). The safety profile of atezolizumab was consistent with prior experience with this treatment as single agent across indications and lines of therapy. Overall, IMpower010 is the first phase III study of cancer immunotherapy to demonstrate DFS improvement in the adjuvant NSCLC setting after platinum-based chemotherapy. The authors concluded that atezolizumab can be considered a practice-changing adjuvant treatment option for patients with PD-L1 TC ≥ 1 % stage II-IIIA non-small-cell lung tumors.

Addition of neoadjuvant nivolumab

The randomized, phase III CheckMate 816 trial tested neoadjuvant use of nivolumab plus chemotherapy against chemotherapy alone in patients with newly diagnosed, resectable, stage IB-IIIA NSCLC. Forde et al. demonstrated that the combination yielded significant improvement in the primary endpoint of pathological complete response (pCR) while maintaining a tolerable safety profile [2]. At ASCO 2021, additional efficacy data and key surgical outcomes were reported [3].

Among the 179 patients randomized into each arm, a numerically greater proportion of those treated with nivolumab had definitive surgery (83 % vs. 75 %); in this group, fewer patients underwent pneumonectomy, and minimally invasive surgery was used more often. Baseline stage of disease did not affect pCR improvement. In stage IB/II, the median residual viable tumor percentages were 28 % vs. 79 % for nivolumab plus chemotherapy vs. chemotherapy; for stage IIIA, this was 8 % vs. 70 %. No differences occurred with respect to completeness of resection, although there was a numerical advantage in the experimental arm regarding R0 resections.

The neoadjuvant nivolumab plus chemotherapy regimen proved tolerable, and the addition of the PD-1 inhibitor did not increase the rate of post-surgical complications. Any-grade surgery-related adverse events were observed in 41 % vs. 47 %. Overall, the safety and surgical outcome data reported thus far from CheckMate 816, along with significant improvement in pCR, support the combination of nivolumab and chemotherapy as a potential neoadjuvant option for patients with resectable NSCLC. The study continues to mature for the other primary endpoint of event-free survival and further outcomes.

Gefitinib vs. chemotherapy in *EGFR*-mutant NSCLC

Although adjuvant cisplatin-based chemotherapy is a standard of care for patients with stage II-III, completely resected NSCLC, relapses are frequent. The randomized, phase III IMPACT trial conducted in Japan tested the assumption that adjuvant EGFR-TKI treatment improves the outcomes of patients with *EGFR*-mutated tumors [4]. In this study, patients after complete resection of stage II-III tumors were randomized to either gefitinib 250 mg/d for 24 months or cisplatin plus vinorelbine every 3 weeks for 4 cycles. Each arm included 116 individuals.

IMPACT did not meet its primary endpoint, as DFS was not significantly prolonged with gefitinib compared to chemotherapy (35.9 vs. 25.0 months; HR, 0.92; p = 0.63). At 5 years, 31.8 % vs. 34.1 % of patients were disease-free. However, according to the exploratory subgroup analysis, some patients such as those aged ≥ 70 years benefited from gefitinib. The OS analysis showed no difference, with almost superimposable curves. Again, the subgroup analysis demonstrated a benefit of the EGFR inhibition in the group aged ≥ 70 years.

Adjuvant gefitinib had acceptable toxicity. While grade 3/4 neutropenia and leukopenia were frequent in the cisplatin/vinorelbine-treated arm, this was negligible in the gefitinib arm where transaminase elevations and rash were most prevalent. Three treatment-related deaths occurred in the cisplatin/vinorelbine group due to cerebral infarction, suicide, and pneumonia. As the authors noted in their conclusion, the apparent non-inferiority of adjuvant gefitinib regarding DFS and OS might justify its use in selected subsets of patients, especially those deemed unsuitable for adjuvant chemotherapy with cisplatin/vinorelbine.

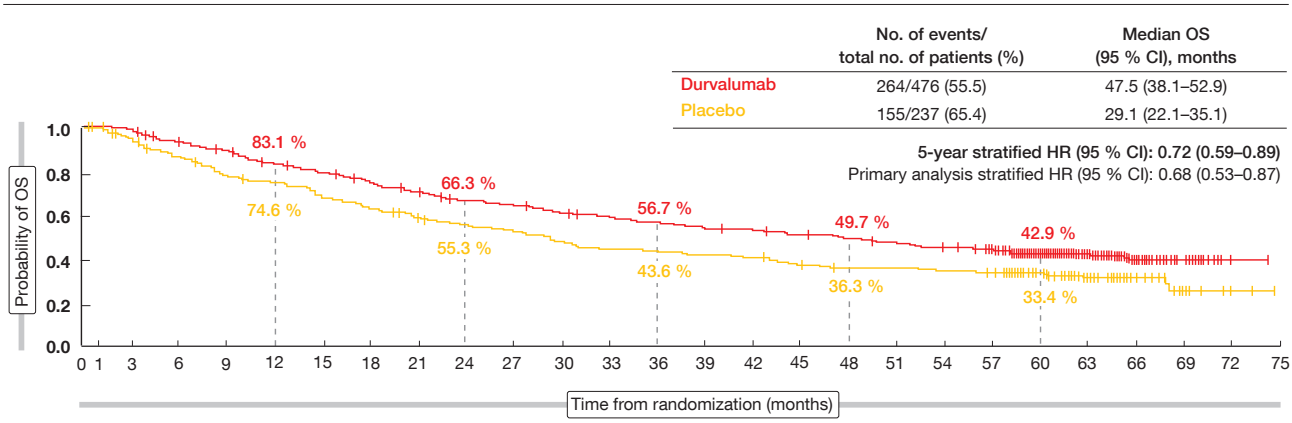

Figure 2: Long-term overall survival benefit with durvalumab vs. placebo in the PACIFIC trial

Lasting benefits at 5 years: PACIFIC

The randomized, double-blind, placebo-controlled, phase III PACIFIC trial has transformed the treatment of patients with unresectable stage III NSCLC whose disease has not progressed after platinum-based chemoradiation. In this setting, the anti-PD-L1 antibody durvalumab, when compared to placebo, significantly improved OS ($p = 0.00251$) and PFS ($p < 0.0001$) and was therefore established as a standard of care [5, 6]. Exploratory survival analyses were conducted approximately 5 years after the last patient had been randomized [7].

At that time, the median follow-up in all randomized patients was 34.2 months. The data showed that the OS and PFS benefits with durvalumab vs. placebo were consistent with the primary analyses [5, 6]. At 5 years, patients in the experimental arm still experienced a 28 % mortality risk reduction, with OS rates of 42.9 % vs. 33.4 % **(Figure 2)**. For PFS, the 5-year rates were 33.1 % vs. 19.0 %, which translated into a 45 % reduction in the risk of progression or death. Likewise, updated OS and PFS for the subgroups were consistent with the results reported at the time of the primary analyses.

The authors noted that these findings demonstrate robust and sustained OS benefit and durable PFS benefit with the PACIFIC regimen. Approximately one third of the durvalumab-treated patients remained alive and free of disease progression at 5 years, which establishes a new benchmark for the standard of care in this setting.

ctDNA as predictor of early relapse

Liquid biopsies based on circulating tumor DNA (ctDNA) analysis are being investigated with the aim of detecting residual disease and recurrence in patients with localized NSCLC. The assessment of minimal residual disease might help to identify patients who may benefit from adjuvant therapy. Therefore, Gale et al. evaluated ctDNA in serial plasma samples using a personalized sequencing assay to explore the feasibility and prognostic value of ctDNA detection at or before relapse in stage IA-IIIB NSCLC patients after treatment with curative intent [8]. Eighty-eight individuals were included; 78.4 % of them underwent surgery, and 21.6 % received chemoradiation. Tumor exome sequencing was performed to identify somatic mutations, and a personalized ctDNA assay was developed for each patient. Plasma samples were collected before and after treatment, and at 3, 6, and 9 months. For 17 patients, additional plasma was collected at the time of disease progression. The patients were followed for a median of 3 years.

According to the findings, residual ctDNA predicts early relapse. Monitoring ctDNA at or prior to relapse using a sensitive patient-specific plasma sequencing assay proved feasible. ctDNA detection 2 weeks to 4 months after the end of treatment was associated with shorter relapse-free survival (HR, 14.8; $p < 10^{-5}$) and OS (HR, 5.48; $p < 0.0003$). In patients who progressed, detection of ctDNA preceded clinical progression by a median lead time of 212.5 days.

Overall, these results support emerging evidence that ctDNA monitoring can reliably detect residual disease after treatment with curative intent many months before clinical progression and offers an opportunity to identify patients who might benefit from adjuvant therapy. ■

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EGFR-mutant disease: strategies against sensitizing and resistance-mediating mutations

Targeting HER3: patritumab deruxtecan

EGFR tyrosine kinase inhibitors (TKIs) are the established first-line option in patients with *EGFR*-mutated NSCLC, although resistance inevitably develops in the long run. A wide variety of genomic alterations has been identified in the context of EGFR TKI resistance [1, 2]. HER3, which is expressed in 83 % of NSCLC tumors [3], is not known to confer resistance to EGFR TKI therapy in *EGFR*-mutant disease. Therefore, the antibody-drug conjugate patritumab deruxtecan (HER3-Dxd) that targets HER3 is a potentially active subsequent option after failure of EGFR TKI treatment.

The phase I U31402-A-U102 dose escalation and dose expansion study tested HER3-Dxd in patients with EGFR-TKI–resistant NSCLC. At ASCO 2021, Jänne et al. reported the pooled efficacy results for 57 patients treated with 5.6 mg/kg in the trial. Safety was presented for a total of 81 individuals; this group included all patients in dose escalation and in dose expansion Cohort 1 (i.e., pretreated patients with adenocarcinoma histology and *EGFR* mutations) [4]. The entire population had received a median of four prior treatment lines. Platin-based chemotherapy had been administered in 91 % and 80 % in the efficacy and safety populations, respectively.

Efficacy across resistance mechanisms

Despite being heavily pretreated, the patients experienced clinically meaningful, durable antitumor effects. HER3-Dxd gave rise to a confirmed ORR of 39 % and a disease control rate (DCR) of 72 %. Responses lasted for a median of 6.9 months, and median PFS was 8.2 months. The subgroup of patients pretreated with osimertinib and platinum-based chemotherapy demonstrated similar efficacy; here, ORR, DCR, and median PFS were 39 %, 68 %, and 8.2 months, respectively. HER3-Dxd proved active across diverse EGFR resistance mechanisms, as well as across the spectrum of baseline HER3 expression according to membrane H scores. HER3 was expressed in the tumors of all evaluable patients and showed no correlation with time since the last EGFR TKI dose. Moreover, the treatment was efficacious irrespective of the presence of CNS metastases.

Forty of the 57 patients in the efficacy population had detectable *EGFR* exon 19 deletions or L858R mutations in plasma at baseline. Early clearance of these aberrations at week 3 or 6, as compared to no clearance, was associated with improved best response **(Figure 1)** and prolonged PFS (8.3 vs. 4.4 months; HR, 0.33). HER3-Dxd showed a manageable safety profile. Treatment discontinuation rates due to treatment-emergent AEs (TEAEs) were low at 11 % and 9 % in the 5.6 mg/kg and all-doses populations, respectively. Among grade ≥ 3 TEAEs, decreases in platelet and neutrophil counts occurred most commonly. There was a low rate of treatment-related interstitial lung disease events (5 % in the total population), with none being grade 4/5. HER3-Dxd is being further assessed in the setting of *EGFR*-mutant NSCLC.

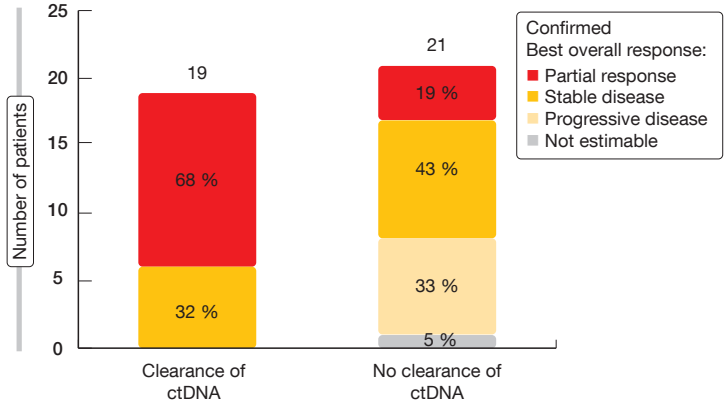

Figure 1: Improved patient responses observed with early clearance of exon 19 deletions and L858R mutations in ctDNA on treatment with patritumab deruxtecan

Amivantamab/lazertinib after osimertinib

In patients who have developed disease progression on treatment with the third-generation TKI osimertinib, resistance mutations are most commonly either EGFR-dependent (e.g., *C797S* mutation) or MET-dependent (e.g., *MET* amplification) [5, 6]. Other pathways such as PIK3CA or RAS/RAF may also be involved, although in 40-50 %, no resistance mechanisms can be identified. Co-occurrence of multiple mechanisms is common.

A potential treatment approach after osimertinib failure is the combination of amivantamab, a bispecific antibody targeting EGFR and MET, with the potent third-generation EGFR TKI lazertinib. Both agents have shown clinical activity across various *EGFR* mutations [7-11]. Based on these observations, 45 chemotherapy-naïve patients with *EGFR* exon 19 deletions or L858R mutations who had progressed on osimertinib were treated with amivantamab plus lazertinib in the dose-expansion phase of the phase I CHRYSALIS trial. Amivantamab was administered intravenously 2-weekly from cycle 2 at doses of 1,050 mg (< 80 kg body weight) or 1,400 mg (≥ 80 kg), while lazertinib 240 mg was taken orally every day.

The analysis presented at ASCO 2021 demonstrated durable responses of this combination [12]. After a median follow-up of 11.0 months, the ORR was 36 %, and 64 % of patients showed clinical benefit (i.e., complete or partial re-

TABLE 1
Outcomes obtained with amivantamab/lazertinib in patients with and without EGFR/MET-based resistance and in patients with MET/EGFR expression

Subgroup	Overall response rate (%)	Median duration of response (months)	Clinical benefit rate (%)	Median progression-free survival (months)
Patients with identified EGFR/MET-based resistance (NGS) n = 17	47	10.4	82	6.7
Patients without identified EGFR/MET-based resistance (NGS) n = 28	29	8.3	54	4.1
Patients with EGFR/MET expression (IHC staining) n = 10	90	9.7	100	12.5

sponses plus stable disease ≥ 11 weeks). Responses lasted for a median of 9.6 months; 69 % of patients responded for at least 6 months. Median PFS was 4.9 months. At the same time, the analysis revealed manageable safety of the regimen. The most common AEs were infusion-related reactions, rash, and paronychia, with the majority rated as grade 1 or 2. Treatment-related dose reductions and discontinuations occurred in 18 % and 4 %, respectively.

Patient selection according to NGS and IHC

The design of the CHRYSALIS trial included biomarker analyses using next-generations sequencing (NGS) and immunohistochemistry (IHC). According to NGS, 17 of 45 patients had EGFR- or MET-based resistance. Among the remaining 28 patients, 12 had identifiable alterations such as the *PIK3CA* E545K mutation or *CCND1* amplification. Those with EGFR/MET-based resistance, compared to those without, fared better regarding ORR, duration of response, clinical benefit rate, and PFS **(Table 1)**. However, NGS did not identify half of the confirmed responders.
In 20 cases, tumor biopsies were sufficient for IHC staining after NGS. Here, 10 patients had combined EGFR/MET H scores ≥ 400, and this group experienced excellent outcomes **(Table 1)**. IHC was shown to identify patients regardless of the underlying genetic resistance mechanisms. The authors therefore suggested that EGFR/MET expression according to IHC might be used as an alternative approach to identify potential responders. The phase I/Ib CHRYSALIS-2 study will seek to validate these biomarkers prospectively in a new osimertinib-pretreated cohort (NCT04077463).

MET amplification: comparison of strategies

Although *MET* amplification is an important mechanism of acquired resistance to EGFR TKI therapy, no treatment standard for progressive disease based on this aberration exists. Three strategies are commonly administered: EGFR-TKI and MET-TKI combination therapy, MET-TKI monotherapy, or chemotherapy. A real-world study compared these three approaches in 70 patients with *EGFR*-mutant NSCLC and acquired *MET* amplification [13]. Treatment consisted of either EGFR TKI therapy plus crizotinib (n = 38), crizotinib alone (n = 10), or chemotherapy (n = 22).

The combination showed the most favorable results across the entire cohort. Compared to chemotherapy, significant superiority was observed with respect to ORR (p = 0.026), DCR (p = 0.016), and PFS (p = 0.036). OS was comparable across the three groups. Moreover, the EGFR TKI plus crizotinib approach showed activity in patients with concurrent *TP53* mutations or *EGFR* amplification, which were the most common concurrent mutations in the three cohorts. As the authors noted, combined EGFR and MET inhibition might be a preferred option in this subset of patients.

Favorable findings for sequential afatinib-osimertinib

The T790M mutation emerges as the predominant resistance mechanism after failure of first- and second-generation EGFR TKIs in approximately 50-70 % of cases [14-17]. As is known, T790M can be targeted effectively using osimertinib. Sequential administration of afatinib and osimertinib has been shown to facilitate prolonged, chemotherapy-free treatment in patients with T790M resistance [18]. Real-world data from South Korea reported at ASCO 2021 assessed time on treatment in four groups of patients receiving first-line afatinib therapy: those in whom subsequent osimertinib was prescribed based on the presence of T790M (Cohort A; n = 116); those with other subsequent treatments in the absence of T790M (Cohort B; n = 143); those with other treatments and unknown T790M status (Cohort C; n = 111); and patients treated with afatinib only who had not received any second-line therapy yet (Cohort D; n = 367) [19].

Median time on treatment (TOT) was 23.42 months in the total study population. For Cohorts A-C, median TOTs in the first-line setting were 17.43, 14.19 and 7.13 months, respectively, thus demonstrating the most favorable outcome for the afatinib-osimertinib sequence. TOT in Cohort D was 42.61 months, which suggests that first-line afatinib allows certain patients to maintain long-term, chemotherapy-free disease control. In the second line, Cohort A again showed the best outcome with a TOT of 11.04 months; for Cohorts B and C, these were 3.32 and 2.43 months, respectively.

Similarly, response rates were highest in Cohort A in the first and second lines. Among the patients who progressed on afatinib treatment, rebiopsy was performed in 70.81 %. Here, the detection rate of T790M was 44.27 %. According to the conclusion of the authors, afatinib followed by osimertinib after the acquisition of the T790M resistance mutation is a feasible and effective strategy.

Outcomes in patients with exon 20 insertion

Among *EGFR* mutations, exon 20 insertion mutations (Exon20ins) are the third

most common alterations, occurring in up to 12 % of cases [20, 21]. At present, no approved targeted therapies are available for lung cancer patients with Exon20ins in the metastatic setting. Limited activity has been observed for EGFR TKIs, platinum-based chemotherapy, docetaxel, and immunotherapies [22-28].

The retrospective real-world study conducted by Chouaid et al. described treatment patterns and clinical outcomes of patients with advanced non-squamous NSCLC harboring *EGFR* Exon20ins [29]. The data source was the French Epidemiological Strategy and Medical Economics Advanced and Metastatic Lung Cancer Data Platform. Among a total of 13,737 patients, four cohorts were defined based on *EGFR* mutation status: Exon20ins without exon 19 deletion/L858R mutation (n = 61); common *EGFR* mutation (i.e., exon 19 deletion or L858R without Exon20ins; n = 1,049); other *EGFR* mutation(s) (n = 439); wild-type *EGFR* mutation or not tested (n = 12,188).

The group with Exon20ins represented 3.9 % of the total, which confirmed that this is a rare aberration in NSCLC patients. In this cohort, first-line chemotherapy was administered in 74.1 %, EGFR TKI treatment in 13.7 %, and immunotherapy in 8.6 %. Patient prognosis was similar to that of the group who had wild-type *EGFR* mutation or had not been tested, which was worse than prognosis for those with common or other *EGFR* mutations **(Table 2)**. Compared to patients with common *EGFR* mutations, median OS was significantly shorter (24.3 vs. 35.4 months; p = 0.049), as was median PFS (7.0 vs. 8.9 months; p = 0.0167). The authors pointed out that these observations highlight the need for therapeutic advancements in patients with exon 20 insertion mutations.

Mobocertinib following platinum pretreatment

The oral, first-in-class, irreversible EGFR TKI mobocertinib has been developed to inhibit *EGFR* Exon20ins and other *EGFR* mutations with or without T790M. Mobocertinib is undergoing clinical assessment in a total of seven cohorts included in a phase I/II study. At ASCO 2021, Ramalingam et al. reported updated primary efficacy results for platinum-pretreated patients (PPP; i.e., patients with Exon20ins-positive metastatic NSCLC after platinum therapy who receive mobocertinib 160 mg/d in the dose-escalation, expansion, or the EXCLAIM cohort) and the EXCLAIM cohort (i.e., previously treated patients with Exon20ins-positive metastatic NSCLC who receive mobocertinib 160 mg/d) [30]. The PPP and EXCLAIM cohorts comprise 114 and 96 individuals, respectively.

Mobocertinib induced deep and durable responses. ORR was 28 % and 25 % according to independent review committee for the PPP and EXCLAIM cohorts, respectively. Almost 80 % in both groups achieved disease control (78 % and 76 %, respectively). In the PPP cohort, median duration of response was 17.5 months, while this had not been reached in the EXCLAIM cohort yet. Median PFS and OS in the PPP cohort amounted to 7.3 and 24.0 months, respectively.

Responses occurred independent of pretreatment and across Exon20ins subtypes regardless of their frequency or position from the C-helix. Consistent with the known safety profile of EGFR TKIs, the AEs elicited by mobocertinib mainly included manageable gastrointestinal and cutaneous events. Dose reductions due to AEs occurred in 25 % and 22 % in the PPP and EXCLAIM cohorts, respectively. In 17 % and 10 %, respectively, treatment had to be discontinued.

Patient-reported outcomes were assessed in the EXCLAIM cohort using the EORTC QLQ-LC13 and EORTC QLQ-C30 questionnaires. This showed that clinically meaningful improvements from baseline for dyspnea, cough, and chest pain were evident in cycle 2 and were maintained throughout the treatment. Likewise, mean global health status/quality of life scores were maintained over the study period despite worsening in gastrointestinal-related symptom scores during treatment. In their summary, the authors stated that mobocertinib appears to have a favorable risk-benefit profile in patients with previously treated *EGFR* Exon20ins-positive metastatic NSCLC and might provide a meaningful treatment option in this population that has a high unmet need.

TABLE 2
Inferior overall survival and progression-free survival in patients with *EGFR* exon 20 insertion mutations compared to those with other mutations

	EGFR exon 20 insertion (n = 61)	Common *EGFR* mutation (n = 1,049)	Other *EGFR* mutation (n = 439)	*EGFR* wildtype/not tested (n = 12,188)
Overall survival				
Median OS, months	24.3	35.4	41.7	20.7
12-month OS rate, %	82.5	83.3	83.4	62.9
24-month OS rate, %	52.6	66.1	66.9	46.5
36-month OS rate, %	27.1	48.8	52.4	36.1
Progression-free survival				
Median PFS, months	7.0	8.9	8.3	5.4
12-month PFS rate, %	24.3	35.8	35.3	24.4
24-month PFS rate, %	4.4	13.0	14.4	12.1
36-month PFS rate, %	4.4	4.3	7.5	7.1

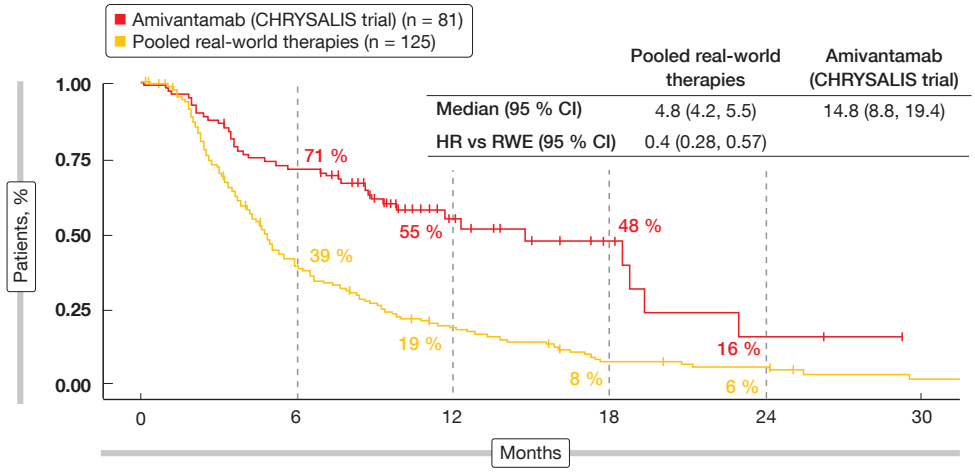

Figure 2: Time to next treatment with single-agent amivantamab in patients with *EGFR* exon 20 insertion mutations compared to real-world outcomes from three databases

Amivantamab in Exon20ins-positive disease

In the CHRYSALIS trial, amivantamab monotherapy has shown durable responses in patients with advanced NSCLC and *EGFR* Exon20ins [8, 9]. Minchom et al. evaluated the efficacy of amivantamab *versus* physician's choice of anticancer treatment in the real-world setting in lung cancer patients with Exon20ins who had received prior platinum-based chemotherapy [31]. To this end, the investigators compared an efficacy analysis set of 81 post-platinum patients from the Exon20ins population included in CHRYSALIS with an external control analysis set (n = 174) derived from three real-world US-based datasets. The control patients met relevant eligibility criteria for the CHRYSALIS study. Their most common therapies were non-platinum-based chemotherapies, immunotherapies, platinum-containing regimens, and EGFR TKIs.

Compared to the real-world cohort, amivantamab-treated patients experienced a 53 % reduction in the risk of progression (median PFS, 8.3 vs. 2.9 months; HR, 0.47) and a 51 % mortality reduction (median OS, 22.8 vs. 12.8 months; HR, 0.49). Time to next treatment was prolonged by 10 months (14.8 vs. 4.8 months; HR, 0.40; **Figure 2**). As the authors noted, the poor performance of the external controls reflected the ineffectiveness of currently available real-world treatments and highlights the urgent need to identify more targeted treatments for patients with advanced NSCLC and *EGFR* Exon20ins.

Uncommon mutations in the real world

EGFR mutations classified as uncommon, i.e., those that are not deletion 19 or L858R mutation, are estimated to represent 7 %-23 % of the *EGFR* mutation pool [32]. "Major" uncommon mutations sensitive to TKI therapy include G719X, S768I, and L861Q. Exon20ins mutations are considered resistant to EGFR TKIs, although this is a highly heterogeneous group. T790M is known to confer resistance to first- and second-generation TKIs. For other uncommon mutations, little data have been obtained on TKI sensitivity. In addition, up to one third of *EGFR*-mutant tumors harbor compound mutations. It can be expected that the growing use of sensitive sequencing-based detection methods and liquid biopsy will increase the frequency of uncommon mutations detected in real-world clinical practice [33].

The real-world cohort study UpSwinG that was conducted in nine countries across Europe and Asia investigated the treatment and outcomes of patients who had ≥ 1 uncommon *EGFR* mutation and received EGFR TKIs (afatinib, gefitinib, erlotinib, osimertinib) in the first or second line [34]. Overall, 246 individuals were included in the analysis. Most were Asian, and less than 10 % had brain metastases, as active brain metastases constituted an exclusion criterion.

The analysis showed that EGFR TKIs were generally the first-line treatment of choice (91.9 % vs. chemotherapy in 8.1 %). Afatinib was the most commonly used index therapy (54.1 %), followed by gefitinib (28.7 %), erlotinib (14.3 %) and osimertinib (2.9 %). TKI therapy conferred encouraging results for the primary endpoint of time to treatment failure (TTF), OS, and ORR. TTF was 11.3 and 8.8 months for afatinib and first-generation TKIs, respectively, and OS was 24.5 and 24.2 months, respectively. With first-line treatment in general, partial responses were obtained in 43.9 %, and stable disease was seen in 41.7 %. Responses to second-line treatment included partial responses and stable disease in 22.2 % and 49.1 %, respectively.

Patient fitness was largely maintained over time; at the start of first-line therapy, half of patients had an ECOG performance status of 1, and at the start of second-line therapy, this proportion had only slightly decreased (45.7 %). Clinical outcomes varied according to the mutation category; TTF and ORRs were generally most favorable in the subgroups with major uncommon mutations and compound mutations. The authors concluded that treatment with an EGFR TKI should be considered for most patients whose tumors harbor uncommon *EGFR* mutations.

First-line benefit of aumolertinib

Aumolertinib is a novel, irreversible, third-generation EGFR TKI that selectively inhibits both sensitizing and resistance *EGFR* mutations. Approval of this drug was granted in China in 2020 based on the APOLLO trial, which demonstrated robust efficacy in patients

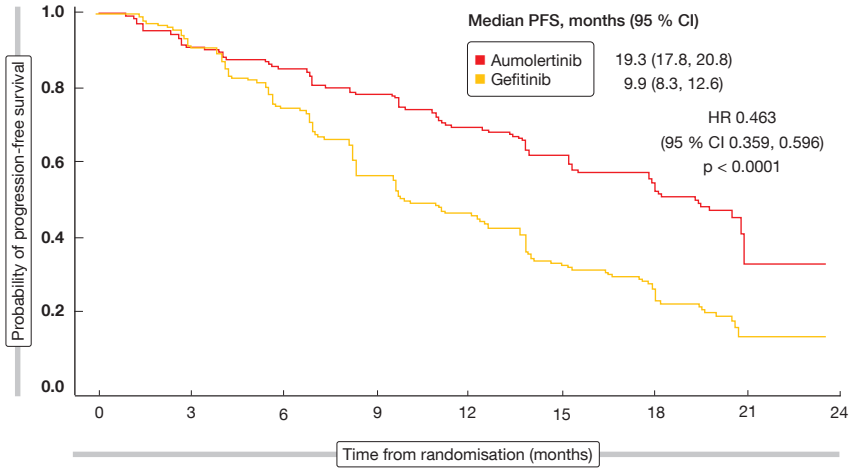

Figure 3: AENEAS trial: first-line superiority for aumolertinib vs. gefitinib regarding progression-free survival

with *EGFR*-mutated NSCLC who had progressed on first- or second-generation EGFR TKIs after developing the T790M mutation [35]. In the first-line setting, the randomized, double-blind, phase III AENEAS trial tested aumolertinib 110 mg/d (n = 214) against gefitinib 250 mg/d (n = 215) in patients with locally advanced or metastatic NSCLC harboring exon 19 deletion or L858R mutation [36].

Compared to gefinitib, aumolertinib gave rise to marked PFS improvement (median PFS, 19.3 vs. 9.9 months; HR, 0.463; p < 0.0001; **Figure 3**). At 12 months, PFS rates were 69.5 % vs. 46.3 %, and at 24 months, 32.5 % vs. 12.9 %. PFS benefits were preserved across subgroups relating to type of *EGFR* mutation, presence of brain lesions, gender, age, smoking history, and ECOG performance score. Median OS had not been reached in either arm yet (HR, 0.82). No difference resulted for ORR (73.8 % vs. 72.1 %), although duration of response was significantly longer in the experimental arm (18.1 vs. 8.3 months; HR, 0.38; p < 0.0001).

Aumolertinib was generally well tolerated. Most commonly, patients experienced creatine phosphokinase elevations, transaminase elevations, and cytopenia. Rash was observed less frequently with aumolertinib than with gefitinib (23.4 % vs. 41.4 %), which also applied to diarrhea (16.4 % vs. 35.8 %). QTc prolongation was seen in 10.7 % with aumolertinib (grade ≥ 3, 0.9 %) vs. 8.8 % with gefitinib (grade ≥ 3, 1.9 %). Interstitial lung disease occurred in 0.9 % vs. 0.5 % (no grade ≥ 3 events in either arm).

In their summary, the authors noted that based on these results, they will pursue discussions with global regulatory authorities with the goal of facilitating a markedly less costly global access pricing structure. Global trials of aumolertinib with chemotherapy and selected targeted agents as well as assessment of the drug in the adjuvant setting are ongoing or planned. ■

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KRAS, MET, ROS1, HER2: current perspectives

CodeBreaK100: sotorasib

Approximately 13 % of patients with adenocarcinoma of the lung harbor the *KRAS*^{G12C} mutation [1]. To date, no agent targeting this oncogenic driver has been licensed, although there is a need to improve outcomes in this population after progression on first-line treatment encompassing immune checkpoint inhibitors. The first-in-class, irreversible, selective KRAS^{G12C} inhibitor sotorasib has demonstrated durable clinical benefit in pretreated patients with *KRAS*^{G12C}-mutated, locally advanced or metastatic NSCLC in the single-arm phase II CodeBreaK100 trial [2]. In this study, 126 patients received sotorasib at a daily oral dose of 960 mg. Eighty-one percent of the participants were previously treated with both platinum-based chemotherapy and immunotherapy. At ASCO 2021, Skoulidis et al. presented updated efficacy and safety data including mature overall survival after a median follow-up of 15.3 months and reported outcomes across various patient subgroups [3].

Sotorasib continued to provide durable clinical benefit with median OS of 12.5 months and median PFS of 6.8 months. Overall, 37.1 % of patients responded, with 4 patients (3.2 %) achieving complete responses. Disease control was obtained in 80.6 %, and median duration of response was 11.1 months. Treatment-related AEs (TRAEs) were mostly grade 1/2 and proved generally manageable. Grade 3 TRAEs occurred in 19.8 % of patients. Diarrhea, nausea and elevated transaminases were observed most commonly. Dose modifications and discontinuations resulted in 22.2 % and 7.1 %, respectively.

TABLE 1
Outcomes in CodeBreak100 according to *STK11* and *KEAP1* mutation status

STK11 status	*KEAP1* status	n	Progression-free survival, months	Overall survival, months	Objective response rate, %
Mutated	Mutated	13	2.6	4.8	23
Mutated	Wildtype	22	11.0	15.3	50
Wildtype	Mutated	7	5.5	7.5	14
Wildtype	Wildtype	62	6.8	Not evaluable	42
All evaluable patient	All evaluable patients	104	6.3	13.1	39

The treatment with sotorasib exhibited broad and consistent clinical activity across a range of patient subgroups. ORR and median OS were favorable irrespective of baseline characteristics including age, number of prior lines of therapy, and type of pretreatment. Notably, in 13 patients after immune checkpoint inhibition who had not been exposed to platinum-based chemotherapy, sotorasib yielded an ORR of 69.2 %, with median OS of 17.7 months.

Improved activity in *STK11*-mutant disease

The prespecified exploratory analyses included the assessment of sotorasib in molecularly defined subgroups. These showed that the likelihood of achieving ORR was independent of *KRAS*^{G12C} mutant allele frequency. Moreover, ORRs did not vary across 84 patients with high or low tumor mutational burden (defined as ≥ 10 vs. < 10 mut/mb). Endpoints were also evaluated by co-occurring mutations in *STK11* and *KEAP1* (n = 104). This is of clinical relevance as inactivating somatic mutations in these genes have previously been linked to worse patient outcomes with standard-of-care therapies including chemotherapy and immunotherapy.

Here, improved efficacy of sotorasib treatment was seen in the *STK11*-mutant group with concurrent wild-type *KEAP1*, with an ORR of 50 %, which numerically exceeded the 39 % ORR in all evaluable patients. Median PFS in this group was 11.0 months compared to 6.8 months in patients with *STK11* and *KEAP1* wildtype and 6.3 months in the

overall cohort **(Table 1)**. Likewise, median OS was longest in the population harboring *STK11* mutations and *KEAP1* wildtype. *KEAP1*-mutant groups, on the other hand, appeared to derive less benefit from sotorasib treatment. However, these analyses are limited due to their exploratory nature and the small sample size. At present, the confirmatory phase III CodeBreaK200 trial evaluating sotorasib *versus* docetaxel in pretreated $KRAS^{G12C}$-mutated NSCLC is ongoing (NCT04303780).

Capmatinib: update of GEOMETRY mono-1

In the open-label, multi-cohort, phase II GEOMETRY mono-1 study, the oral, highly potent and selective MET inhibitor capmatinib has demonstrated clinically meaningful efficacy in patients with stage IIIB/IV NSCLC and *MET* exon 14 skipping mutations (*MET*ex14) [4]. Capmatinib has been approved in several countries for the treatment of patients with advanced *MET*ex14-positive NSCLC. GEOMETRY mono-1, which also enrolled patients with *MET* amplification, contains four *MET*ex14 cohorts: Cohort 5b and expansion Cohort 7 include treatment-naïve patients, while in Cohort 4 and expansion Cohort 6, pretreated patients are being evaluated. Overall, 160 patients were allocated to the four groups. At ASCO 2021, Wolf et al. reported preliminary data for Cohort 7 (n = 32) as well as other updated results [5].

According to the analysis, the ORR was 65.6 % in this group, which was in line with the previously reported ORR of 67.9 % for Cohort 5b [4]. Median PFS was 10.8 months in Cohort 7, while median OS had not been reached yet. Clinically meaningful OS results were obtained for treatment-naïve patients from Cohort 5b and pretreated patients from Cohort 4, in whom median OS was 20.8 and 13.6 months, respectively. The authors emphasized the long-term survival benefit conferred by capmatinib in these populations. Cohort 4 that contained patients treated in the second and third lines showed an ORR of 40.6 %. In Cohort 6, which was restricted to the second-line setting, ORR was 51.6 %. Responses occurred early on.

The manageable safety profile of capmatinib remained unchanged after the prolonged follow-up. Among treatment-related AEs, peripheral edema and nausea were most common (any grade, 46.1 % and 34.3 %, respectively). Four treatment-related fatal serious AEs occurred (i.e., cardiac arrest, hepatitis, organizing pneumonia, pneumonitis). In their conclusion, the authors noted that these updated results further confirm *MET*ex14 as a targetable oncogenic driver in NSCLC and strengthen the evidence for capmatinib as a valuable option in this setting.

Tepotinib for patients with *MET* amplification

Lung cancer patients harboring *MET* amplification, which is present as an oncogenic driver in 1-5 % of NSCLC cases [6], have poor prognosis [7]. There is an urgent unmet need for new treatments in this population. The highly selective, oral, once daily MET inhibitor tepotinib has been approved for the treatment of metastatic NSCLC with *MET*ex14 in Japan and the US based on Cohort A of the open-label, multicenter, phase II VISION trial [8, 9]. At ASCO 2021, Le et al. reported the first data from Cohort B, which assessed tepotinib in patients with advanced NSCLC and *MET* amplification, as detected by liquid biopsy, in the absence of *MET*ex14 [10]. Patients enrolled in Cohort B had *EGFR* and *ALK* wildtype and were treated in the first, second or third line. Prior immunotherapy was allowed. Overall, 24 individuals received tepotinib 500 mg/d, which was predominantly administered in the second line. ORR by independent review committee was defined as the primary endpoint.

In this first study of a MET inhibitor in advanced NSCLC with *MET* amplification prospectively detected by liquid biopsy, tepotinib showed high and clinically meaningful activity. Overall, 41.7 % of patients responded to treatment. Patients receiving tepotinib in the first line appeared to be more sensitive to therapy. Subgroup analyses yielded response rates of 71.4 %, 30.0% and 28.6 % for the first, second, and third lines, respectively **(Table 2)**. In the overall population, median PFS was 4.2 months, with a 9-month PFS rate of 40 %. In the first, second and third lines, the 9-month PFS rates were 51 %, 58 %, and not estimable. Median duration of response was still immature; at 9 months, 67 % of patients had ongoing responses.

Tepotinib was well tolerated, with mostly mild or moderate treatment-related AEs. Peripheral edema was the most common AE (any grade, 37.5 %), followed by generalized edema and constipation. Grade 3/4 treatment-related AEs occurred in 29.2 % but did not give rise to treatment discontinuation. According to the authors, tepotinib warrants further evaluation in patients with *MET*-amplified advanced NSCLC.

ROS1-positive NSCLC: activity of brigatinib

Crizotinib was the first agent to be approved for the treatment of patients with *ROS1*-fusion-positive NSCLC. However, no standard options have been introduced for crizotinib-resistant *ROS1*-positive disease to date. The single-arm, multicenter, phase II basket trial Barossa evaluated the second-generation ALK/ROS1 inhibitor brigatinib in advanced solid tumors with *ROS1* fusion

TABLE 2
Tepotinib in NSCLC with *MET* amplification: objective responses overall and by treatment line

		Overall (n = 24)	First line (n = 7)	Second line (n = 10)	Third line (n = 7)
Best overall response, n (%)	Partial response	10 (41.7)	5 (71.4)	3 (30.0)	2 (28.6)
	Stable disease	1 (4.2)	0	1 (10.0)	0
	Progressive disease	5 (20.8)	1 (14.3)	2 (20.0)	2 (28.6)
	Not evaluable	8 (33.3)	1 (14.3)	4 (40.0)	3 (42.9)
ORR, n (%)		10 (41.7)	5 (71.4)	3 (30.0)	2 (28.6)

positivity. Daga et al. reported the results for Cohort 2 of the study that included 19 crizotinib-pretreated NSCLC patients from 9 institutions. ORR was defined as the primary endpoint [11].

In this group, brigatinib showed modest activity with an ORR of 26.3 % and a disease control rate of 57.9 %. Median PFS assessed by independent review and OS were 7.3 and 12.2 months, respectively. At 1 year, 57.4 % of patients were alive, and 26.9 % were progression-free. The safety profile of brigatinib including diarrhea, transaminase elevations and amylase elevations was consistent with previous studies. No grade 4/5 AEs occurred. Enrollment of the cohort 1 of the Barossa study that contains ROS1-inhibitor–naïve patients is ongoing.

HER2-targeted approach plus docetaxel

Approved therapies are lacking for NSCLC patients with *HER2* aberrations that are oncogenic drivers in 1-2 % of cases [12]. The aim of the multicenter, single-arm, phase II IFCT-1703 R2D2 trial presented by Mazieres et al. was to prospectively evaluate a combination of two HER2-directed antibodies with docetaxel in this setting [13]. Forty-six pretreated patients with stage III/IV NSCLC and *HER2* exon 20 insertion or mutation received pertuzumab 420 mg plus trastuzumab 6 mg/kg and docetaxel 75 mg/m^2 from cycle 2 every 3 weeks.

Confirmed ORR, which was defined as the primary endpoint, was 28.9 % with this regimen. Stable disease resulted in 57.8 %. Median PFS and OS were 6.8 and 17.6 months, with 12-month rates of 29.0 % and 68.3 %, respectively. Treatment-related AEs mainly included diarrhea, fatigue, anemia, nausea, stomatitis, and decreased neutrophil counts. Among grade 3/4 AEs, decreased neutrophil counts occurred most frequently, followed by diarrhea. No pulmonary or cardiac toxicity was observed.

As the authors concluded, the triplet of trastuzumab, pertuzumab and docetaxel is feasible and active in pretreated, advanced, *HER2*-positive NSCLC. These results confirm the activity of HER2-antibody–based strategies which should be considered in these patients. ■

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Immunotherapy: from predictive factors to antibiotics

Update of CheckMate 9LA

Based on the randomized, phase III CheckMate 9LA study, the first-line regimen of nivolumab plus ipilimumab and two cycles of chemotherapy has been approved in the indication of metastatic NSCLC without *EGFR* or *ALK* aberrations in many countries. CheckMate 9LA included approximately 360 patients with stage IV or recurrent disease in each arm and demonstrated significant OS, PFS, and ORR improvements with the immunotherapy-based regimen compared to four cycles of standard chemotherapy [1]. Reck et al. reported updated efficacy and safety findings after a minimum follow-up of 2 years, as well as outcomes in patients who discontinued treatment due to adverse events [2].

For overall survival, which constituted the primary endpoint, the analysis showed durable efficacy of the combination. Median OS was 15.8 vs. 11.0 months (HR, 0.72), with 24-month OS rates of 38 % vs. 26 %. Survival advantages occurred across all subgroups including patients with CNS metastases. Furthermore, PFS and response benefits were maintained with longer follow-up. At 24 months, 20 % vs. 8 % of patients in the experimental and control arms, respectively, were progression-free (HR, 0.67). Median duration of response was 13.0 vs. 5.6 months; here,

the 24-month rates amounted to 34 % vs. 12 %. The combination proved superior to chemotherapy in all PD-L1 expression categories (i.e., < 1 %, ≥ 1 %, ≥ 50 %) in terms of OS, PFS, and response **(Table 1)**. Similarly, patients treated in the experimental arm fared better with respect to OS in both non-squamous and squamous histology subgroups. No new safety signals were observed with longer follow-up. Most grade 3/4 treatment-related AEs (TRAEs) in the experimental arm emerged during the two chemotherapy cycles at the beginning of treatment.

A post-hoc exploratory analysis assessed the outcomes of patients who had discontinued all components of nivolumab/ipilimumab plus chemotherapy due to TRAEs. This showed that discontinuation did not have a negative impact on the long-term benefits. On the contrary, when compared indirectly to the total population randomized to combination treatment, these patients experienced improved survival with median OS of 27.5 months and a 24-month OS rate of 54 %. Fifty-one percent responded to therapy. After discontinuation, median duration of response was 14.5 months, and 56 % maintained their responses for ≥ 1 year. In their summary, the authors noted that these updated results continue to support nivolumab/ipilimumab plus two cycles of chemotherapy as an efficacious first-line treatment option for patients with advanced NSCLC.

Association between irAEs and OS

Immune-related adverse events (irAEs) have been reported in up to 80 % and 95 % of patients receiving checkpoint inhibitor monotherapy and combination therapy, respectively [3]. Increasing evidence suggests that the occurrence of irAEs with PD-(L)1 inhibitor therapy might be predictive of improved outcomes [4-7]. Based on this assumption, the post-hoc exploratory analysis presented by Socinski et al. evaluated the association between irAEs and OS in the IMpower130, IMpower132 and IMpower150 first-line trials [8]. IMpower130 and IMpower132 have assessed atezolizumab plus different chemotherapy regimens, while IMpower150 tested bevacizumab in addition to atezolizumab plus chemotherapy [9-11]. Pooling of the three trials yielded a total of 2,503 patients who had been treated with either atezolizumab-containing regimens (n = 1,577) or control therapies (n = 926). Each of these two groups was divided into patients with and without irAEs.

In the atezolizumab arm, 48 % of patients had any irAEs 11 % of which were grade 3-5. In the control arm, this applied to 32 % and 5 %, respectively. Patients who experienced irAEs demonstrated longer median OS than those without irAEs in both arms. For the atezolizumab arm, this was 25.7 vs. 13.0 months (HR, 0.69), and for the control arm, 20.2 vs. 12.8 months (HR, 0.82). At 1, 3, 6 and 12 months, atezolizumab-treated patients with irAEs showed the most favorable OS findings compared to the other groups. Also, ORR was highest in this cohort (61.1 %) compared to atezolizumab-treated patients without irAEs (37.2 %) and patients in the control arm with irAEs (42.2 %) and without irAEs (34.0 %).

OS was further evaluated by grade of irAEs in the atezolizumab arm. Here, patients with grade 1/2 irAEs experienced more favorable survival at 1, 3, 6 and 12 months than those with grade 3-5 irAEs or those without any irAEs. Patients with grade 3-5 irAEs had the shortest OS, potentially due to treatment disruption or discontinuation. The authors concluded that this analysis suggests an association between irAEs and efficacy in patients with NSCLC and

TABLE 1
Efficacy outcomes in CheckMate 9LA according to PD-L1 expression

	PD-L1 < 1 %	PD-L1 ≥ 1 %	PD-L1 ≥ 50 %
	Nivo/ipi + chemo (n = 135) vs. chemo (n = 129)	Nivo/ipi + chemo (n = 204) vs. chemo (n = 204)	Nivo/ipi + chemo (n = 76) vs. chemo (n = 98)
Overall survival			
Median OS, months	17.7 vs. 9.8 HR, 0.67	15.8 vs. 10.9 HR, 0.70	18.9 vs. 12.9 HR, 0.67
12-month OS rates, %	63 vs. 45	65 vs. 47	70 vs. 51
24-month OS rates, %	37 vs. 22	41 vs. 28	45 vs. 32
Progression-free survival			
Median PFS, months	5.8 vs. 4.9 HR, 0.68	7.0 vs. 5.0 HR, 0.67	7.5 vs. 4.5 HR, 0.59
12-month PFS rates, %	32 vs. 17	34 vs. 18	38 vs. 20
24-month PFS rates, %	20 vs. 5	20 vs. 9	28 vs. 10
Response			
Objective response rate, %	31.1 vs. 20.2	42.6 vs. 27.9	50.0 vs. 31.6
12-month response rate, %	58 vs. 5	49 vs. 30	55 vs. 23
24-month response rate, %	45 vs. 0	33 vs. 13	52 vs. 16
Median duration of response, months	17.5 vs. 4.3	11.8 vs. 5.6	26.0 vs. 5.4

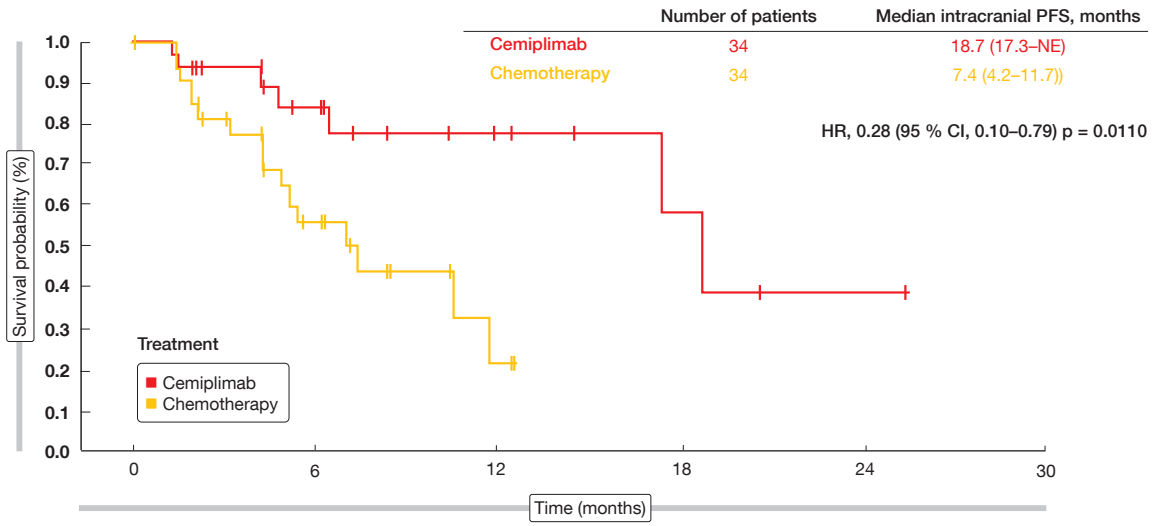

Figure 1: Intracranial progression-free survival with cemiplimab vs. chemotherapy

further supports the use of atezolizumab combined with chemotherapy with or without bevacizumab in the first-line setting.

Dual PD-L1/CTLA-4 inhibition: KN046

The recombinant humanized PD-L1/CTLA-4 bispecific antibody KN046 provides dual CTLA-4 and PD-L1 inhibition and offers reduced treatment-associated toxicity due to limited peripheral distribution. An open-label, multicenter, phase II study was conducted to evaluate KN046 in combination with standard-of-care doublet chemotherapy based on the hypothesis that durable responses and OS benefits can be improved using this combined approach [12]. Patients with stage IV NSCLC who were naïve regarding systemic treatment received KN046 5 mg/kg i. v. every 3 weeks in addition to carboplatin plus either pemetrexed or paclitaxel dependent on histology. Overall, 87 patients participated in the trial, with 51 (56.8 %) and 36 (41.3 %) showing non-squamous and squamous histology, respectively. More than half of the tumors in the total group (55.4 %) expressed PD-L1 (≥ 1 %). ORR and disease control rate (DCR) were defined as the primary endpoint.

Indeed, the regimen demonstrated promising clinical benefit as first-line treatment in stage IV NSCLC, particularly in patients with PD-L1–positive tumors and squamous histology. In the total population, ORR and DCR were 50.6 % and 87.7 %, respectively. For the non-squamous group, this was 45.8 % and 89.6 %, respectively, and for the squamous group, 57.6 % and 84.8 %, respectively. Median PFS in all patients amounted to 5.9 months. Those with squamous histology and PD-L1 ≥ 1 % achieved the longest median PFS of 10.8 months. In the PD-L1–positive, all-histology group, this was 6.7 months. Median OS had not been reached yet, with a 15-month OS rate of 74.9 %.

Among grade ≥ 3 treatment-emergent AEs (TEAEs), diarrhea (5.7 %), alanine aminotransferase increases (4.6 %), infusion-related reactions (3.4 %) and rash (3.4 %) occurred most frequently. Grade ≥ 3 irAEs mostly comprised allergic dermatitis, diarrhea, and rash; overall, 8.0 % of patients developed at least one grade ≥ 3 irAE.

Cemiplimab in CNS disease

The phase III EMPOWER-Lung 1 study was performed to test the highly potent anti-PD-1 antibody cemiplimab as single-agent first-line treatment against chemotherapy according to investigator's choice in patients with advanced NSCLC that showed ≥ 50 % PD-L1 expression. Compared to chemotherapy, the antibody treatment led to significant improvements with respect to OS, PFS, ORR, and duration of response [13]. EMPOWER-Lung 1 included a notable proportion of patients with brain lesions because the protocol permitted treated, clinically stable CNS metastases. Historically, these patients have been underrepresented in clinical trials of first-line PD-(L)1 inhibitors [14-16]. A post-hoc subgroup analysis on the benefit of cemiplimab in patients with brain metastases was reported at ASCO 2021 [17].

At the time of randomization, 68 of 563 patients (12.1 %) had treated stable brain metastases. They were evenly distributed between cemiplimab (n = 34) and chemotherapy (n = 34). In this group, cemiplimab gave rise to an OS advantage with an 83 % risk reduction (18.7 vs. 11.7 months; HR, 0.17; p = 0.0091). Median PFS was almost double, at 10.4 vs. 5.3 months (HR, 0.45; p = 0.0231). For intracranial PFS, the difference was even larger (18.7 vs. 7.4 months; HR, 0.28; p = 0.0110; **Figure 1**). Likewise, ORR by independent review committee in the cemiplimab group markedly exceeded the response rate obtained in the chemotherapy group (41.2 % vs. 8.8 %; OR, 6.9; p = 0.0034). Three patients in the experimental arm (8.8 %) achieved complete responses, while none in the control arm did. In their conclusions, the authors emphasized that the magnitude of clinical benefit observed with cemiplimab in patients with brain metastases compared favorably with the overall EMPOWER-Lung 1 population. Cemiplimab monotherapy was shown to represent a suitable option for this subgroup of patients.

Quality-of-life data for tislelizumab

The anti-PD-1 antibody tislelizumab has been engineered to minimize binding to Fcγ receptors on macrophages, thus abrogating antibody-dependent phagocytosis, which is a potential mechanism of resistance to anti-PD-1 therapies [18, 19]. RATIONALE 303, a randomized, open-label, multicenter, phase III trial, has demonstrated significant OS, PFS and ORR benefits for single-agent tislelizumab compared to docetaxel in patients with NSCLC experiencing progression during or after a platinum-containing regimen [20]. At ASCO 2021, Zhou et al. presented findings on health-related quality of life as assessed in RATIONALE 303 using the EORTC QLQ-C30 and QLQ-LC13 questionnaires [21]. Overall, 805 patients had been randomized. The analyzed population included 784 individuals; among these, 530 and 254 had been treated with tislelizumab and docetaxel, respectively.

Changes in the EORTC QLQ-C30 scores from baseline favored the immune checkpoint inhibition. The patients in the experimental arm experienced improvements regarding global health score/quality of life and fatigue in both cycles 4 and 6 compared with those treated in the control arm. While the physical function domain worsened in the docetaxel arm in cycles 4 and 6, this remained stable with tislelizumab. The difference between treatments became significant in cycle 6. Similarly, compared with docetaxel, the EORTC QLQ-LC13 index score (overall symptoms), cough, and peripheral neuropathy improved significantly in the tislelizumab arm in both cycles 4 and 6. By cycle 6, there was a trend towards significant improvement for dyspnea. No differences occurred with respect to pain measures and hemoptysis. Also, tislelizumab-treated patients experienced a lower risk of deterioration in overall symptoms as indicated by the QLQ-LC13 index score, dyspnea, cough, and peripheral neuropathy.

The symptom improvements were tested using two types of analysis, with the results showing similar patterns. As the authors emphasized, these findings are in line with the clinical and survival benefits observed for tislelizumab [18] as well as other findings on health-related quality of life in the context of PD-1 inhibition [22]. The data add to the favorable risk-benefit ratio of tislelizumab in patients with NSCLC who have progressed on a platinum-containing regimen.

Tislelizumab plus chemotherapy

The open-label, randomized, multicenter phase III RATIONALE 307 trial assessed tislelizumab combined with chemotherapy as first-line treatment of patients with advanced NSCLC of squamous histology [23]. In addition to tislelizumab, Arms A and B received paclitaxel/carboplatin and nab-paclitaxel/carboplatin, respectively. Arm C was treated with paclitaxel/carboplatin. The combined approach significantly improved median PFS, with risk reductions of approximately 50 % for Arm A vs. C and Arm B vs. C ($p < 0.001$ each). Based on RATIONALE 307, tislelizumab has been approved in combination with chemotherapy for the first-line treat-

TABLE 2
Responses and duration of response by independent review committee in patients included in the RATIONALE 307 trial aged ≥ 65 years

	Arm A Tislelizumab + paclitaxel/carboplatin (n = 39)	Arm B Tislelizumab + nab-paclitaxel/carboplatin (n = 52)	Arm C Paclitaxel/carboplatin (n = 36)
ORR, %	69.2	75.0	50.0
Complete response, n (%)	3 (7.7)	2 (3.8)	0 (0.0)
Partial response, n (%)	24 (61.5)	37 (71.2)	18 (50.0)
Duration of response, months	6.9	Not evaluable	6.2
HR	0.694	0.512	

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ment of patients with advanced squamous NSCLC in China. Wang et al. reported a subgroup analysis of the trial conducted in patients aged ≥ 65 years [24]. Among 127 elderly study participants, 39, 52 and 36 had been randomized into Arms A, B, and C, respectively.

Tislelizumab plus chemotherapy elicited significant benefits in this group. PFS was longer in the tislelizumab-treated arms (9.7 months each) than in the chemotherapy-alone arm (5.2 months; HRs, 0.602 and 0.564). ORRs in Arms A and B exceeded the response rate obtained in Arm C **(Table 2)**. The safety profile including irAEs was consistent with the profile observed in the overall population. TEAEs leading to permanent discontinuation of tislelizumab occurred with similar incidence in Arms A and B (15.4 % each). Confirmed immune-related TEAEs were reported in 35.9 % and 34.6 % in Arms A and B, respectively. Most were mild or moderate and did not lead to discontinuation of any treatment component.

Another tislelizumab-based combination is being assessed in the ongoing randomized, double-blind, phase III AdvanTIG-302 trial [25]. This global study will provide insights into the effect of dual targeting with tislelizumab and the anti-TIGIT antibody ociperlimab in patients with PD-L1-high, locally advanced/recurrent or untreated metastatic NSCLC. Anti-TIGIT and anti-PD1 antibodies have been shown to induce synergistic immune cell activation and enhanced antitumor activity [26]. AdvanTIG-302 is comparing ociperlimab plus tislelizumab (Arm A) with pembrolizumab (Arm B) and tislelizumab monotherapy (Arm C). PFS and OS for Arm A vs. Arm B have been defined as the dual primary endpoint.

Microbiome and IO activity

As antibiotic treatment disrupts the native gut microbiome that plays an important role in host response to immunotherapy, antibiotics are assumed to compromise the efficacy of immune checkpoint inhibitors in patients with NSCLC. Stokes et al. further explored this association in a large population from the Veterans Health Administration Database (n = 3,634) in their retrospective cohort study [27]. These patients had been diagnosed with NSCLC from 2010 to 2018 and treated with checkpoint inhibitors. Indeed, receipt of antibiotics within either 30 days before or 60 days after the start of immune checkpoint inhibition was associated with significantly lower survival ($p < 0.0001$). The authors stressed that antibiotics should be used judiciously in NSCLC patients receiving checkpoint inhibitors as they might exert a detrimental effect on outcomes.

Similarly, a prospective, multicentric, observational study related to the intestinal microbiome in the setting of immunotherapy [28]. It has been shown that the presence of the bacterium *Akkermansia muciniphila* correlates with the success of nivolumab treatment [29]. The present study aimed to validate the prognostic significance of *Akkermansia* in patients with advanced NSCLC amenable to immunotherapy in the first and second lines. Stool samples were collected from 311 patients at study entry and analyzed using metagenomics sequencing. *Akkermansia* was detected in 158 cases and absent in 153.

Relative abundance as a predictor

Objective response rate, which constituted the primary endpoint, was higher in the *Akkermansia*-positive group than in the negative population (27 % vs. 17 %). Likewise, most of the patients in the group of those who were alive at 12 months and beyond were *Akkermansia*-positive (57 %). In contrast, only 42 % of those who lived for < 12 months were positive. According to the authors, the presence of *Akkermansia* is indeed a surrogate biomarker of improved outcomes.

However, stratification based on the relative abundance of *Akkermansia* was shown to be a more accurate independent predictor than the binary modality. *Akkermansia* was unexpectedly overrepresented in patients with OS < 12 months within the positive group. The researchers divided the cohort into three groups (negative, low, high) and showed that low relative abundance of *Akkermansia* correlated with increased ORR and OS, while patients with high relative abundance fared worst. Overabundance was more frequent in patients exposed to antibiotics than in those without antibiotic exposure. Patients who had both high relative abun-

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dance of *Akkermansia* and exposure to antibiotics were most likely to have short survival **(Figure 2)**. RNA sequencing of tumor samples at diagnosis revealed increased expression of CD3, VCAM1 and ZBP1, which indicates that *Akkermansia* promotes recirculation of cells in the microenvironment.

The authors concluded that these data provide a rationale to develop a microbiome-based approach to study gut dysbiosis in routine clinical oncology care. The first immunotherapy trial for patients with advanced NSCLC and undetectable intestinal *Akkermansia muciniphila* will be launched by the study group. ■

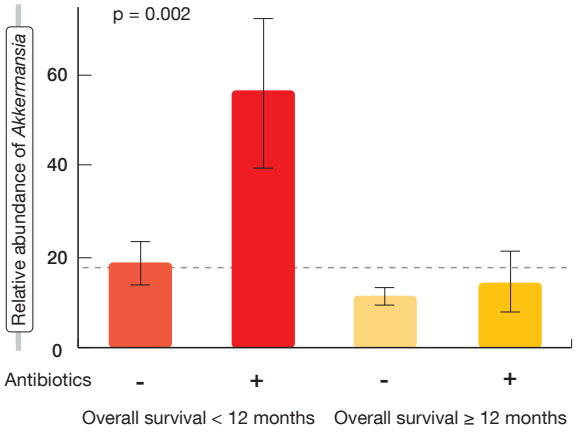

Figure 2: Survival outcomes according to the presence of *Akkermansia muciniphila* and use of antibiotics

How does checkpoint inhibition perform in the setting of oncogene-driven lung cancer?

Impact of various aberrations

Retrospective analyses have demonstrated limited activity of immune checkpoint inhibitors (CPIs) in patients with actionable oncogenic driver mutations [1, 2]. In similar vein, the randomized controlled IMpower150 and IMpower130 studies revealed no survival benefit of adding CPIs to platinum doublets in patients who harbored *EGFR* and *ALK* aberrations [3, 4].

The retrospective study reported by Kelly et al. was conducted to describe PFS and other endpoints with chemotherapy plus CPIs *versus* chemotherapy alone in the setting of oncogene-driven NSCLC [5]. The patients included had at least one driver mutation (*EGFR*, *ALK*, *ROS1*, *MET*, *RET*, *KRAS*, *HER2*, *NTRK*). Between January 2018 and December 2019, they received platinum-based doublet regimens with or without checkpoint inhibition at the NCI-designated University of California Cancer Centers.

Overall, 147 patients were included in the analysis. *EGFR* mutations constituted the most common driver alterations (49.7 %), followed by *KRAS* mutations (36.7 %) and *ALK* fusions (6.8 %). Two percent of patients had *MET* mutations. *HER2* mutations, *RET* fusions and *ROS1* fusions were present in 1.4 % each, and *BRAF* mutations in 0.7 %. PD-L1 expression of 1-49 % and ≥ 50 % was found in 25.2 % and 19.7 %, respectively. Thirty percent of tumors did not express PD-L1, and in 24.5 %, the PD-L1 status was unknown.

Chemotherapy plus immunotherapy, as compared to chemotherapy only, did not confer any significant PFS or OS benefits in either group except for the small cohort with $KRAS^{G12C}$-mutated tumors. In this population, median PFS was 249 vs. 93 days with chemotherapy plus CPIs vs. chemotherapy (HR, 0.31; p = 0.01415). Median OS had not been reached in the immunotherapy-treated patients, while it was 258 days for chemotherapy only (HR, 0.26; p = 0.02542; **Figure**). The analysis identified no new safety concerns.

Moreover, PFS and OS were compared in additional cohorts. These comprised never smokers, current/former smokers, patients on first-line therapy and patients on second- or later-line therapy. In none of these, significant PFS or OS differences were observed for chemotherapy plus immunotherapy vs. chemotherapy. This was also true for the entire cohort where 71 and 76 patients received the combined strategy and chemotherapy alone, respectively. Here, risk reductions for PFS and OS were 7 % (HR, 0.93; p = 0.69832) and 26 % (HR, 0.74; p = 0.18754), respectively.

Anti-PD-(L)1 agents & *KRAS* status

While phase III trials on agents targeting KRAS in patients with *KRAS*-mutant NSCLC are ongoing, the clinical efficacy of anti-PD-(L)1 therapies in this subgroup remains a topic of debate. Therefore, Landre et al. conducted a meta-analysis of randomized studies investigating first-line or second-line anti-PD-(L)1 antibodies with or without chemotherapy vs. chemotherapy alone in patients with advanced *KRAS*-mutant NSCLC [6]. Six trials assessing pembrolizumab, atezolizumab or nivolumab in a total of 4,809 patients were included in the analysis. The proportions of patients with *KRAS*-mutant disease enrolled in these studies ranged between 23 % and 38 %.

Anti-PD-(L)1 therapies with or without chemotherapy were shown to

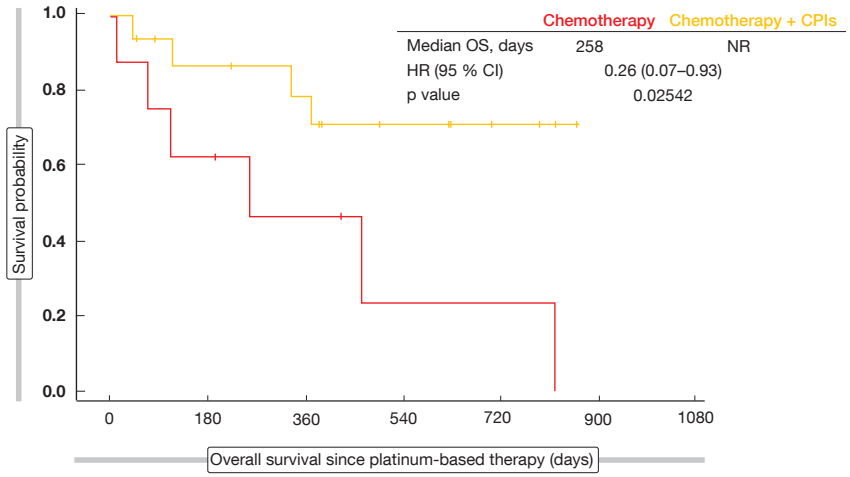

Figure: Overall survival for chemotherapy plus CPIs vs. chemotherapy in patients with *KRAS*^{G12C} mutations

achieve longer OS and PFS than chemotherapy alone in both *KRAS*-mutant and *KRAS*-wildtype patients, with an even greater benefit for the mutated cohort. In this population, the experimental treatment, as compared to chemotherapy, led to a 41 % reduction in mortality risk (HR, 0.59; p < 0.00001) and a 42 % reduction in the risk of progression and death (HR, 0.58; p = 0.0003). OS benefits were observed in both first-line and second-line trials. In the *KRAS*-wildtype population, patients treated with immunotherapy derived a 13 % OS benefit (HR, 0.87). The comparison across the two populations showed that OS for patients with *KRAS* mutation was significantly longer than for patients with *KRAS* wildtype (p = 0.001).

G12C mutations vs. non-G12C mutations

Another analysis related to the efficacy of first-line chemo-immunotherapy regimens in patients with *KRAS*-mutant advanced/metastatic lung cancer treated at the Memorial Sloan Kettering Cancer Center and Dana-Farber Cancer Institute [7]. This group comprised 69 and 93 patients with G12C and non-G12C *KRAS* mutations, respectively. Less than half of tumors in both cohorts were PD-L1–positive. PD-L1 expression of 1-49 % was present in 31 % and 35 % of patients with G12C mutations and non-G12C mutations, respectively; for PD-L1 expression of 50-100 %, this was 12 % and 11 %, respectively.

Patients with G12C mutations, as compared to those with non-G12C mutations, derived greater benefits from chemo-immunotherapy in terms of PFS (6.9 vs. 6.0 months; p = 0.04) and OS (21.3 vs. 14.3 months; p = 0.07). Furthermore, the researchers evaluated the impact of *STK11* and *KEAP1* co-mutations within the G12C-mutated group. Fifty-six percent of patients had neither mutation, while *STK11* was mutated in 15 %, *KEAP1* in 6 %, and both in 23 %. Patients with *STK11* and *KEAP1* wildtype were shown to do considerably better with chemo-immunotherapy than those with *STK11* and/or *KEAP1* mutations. Median PFS for these two groups was 15.8 vs. 5.6 months (p = 0.03). Likewise, wildtype patients developed complete or partial responses more frequently than those harboring mutations, although this difference was not significant (p = 0.11).

In addition to the co-mutation status, PD-L1 expression affected the outcomes to chemo-immunotherapy in the G12C-mutated group. Objective responses were more likely in the presence of PD-L1 positivity compared to PD-L1 negativity, and median PFS was longer (10.7 vs. 6.8 months), although neither of these differences was significant. In their conclusions, the authors noted that co-mutation pattern and PD-L1 expression status might identify patients with *KRAS*-mutated lung cancer most in need of alternative first-line therapies such as KRAS^{G12C} inhibitors.

Real-world data for CPIs & *STK11* co-mutation

These findings were corroborated by real-world evidence reported at ASCO 2021 that assessed the impact of co-occurring *STK11* mutations on outcomes in patients with *KRAS*^{G12C}-mutant adenocarcinoma of the lung treated with a first-line CPI-containing regimen. Heist et al. conducted a retrospective observational real-world study based on Guardant INFORM, which is a nationally representative US healthcare claims clinical-genomic dataset [8]. The researchers identified 330 and 938 patients with and without *KRAS*^{G12C} mutations, respectively. In the *KRAS*^{G12C}-mutated cohort, co-occurring mutations in the *STK11* gene were present in 21 %. The matched cohort without *KRAS*^{G12C} mutation contained patients with other *KRAS* mutations, as well as patients with *KRAS* wildtype; the latter represented 80 % of the group. *STK11* mutations were found in 9 % of those with other *KRAS* muta-

TABLE
Outcomes by *KRAS* mutation and *STK11* co-mutation status

Cohort	Endpoints	HR (95 % CI) *STK11* wildtype vs. *STK11* mutation	p value
KRAS^{G12C} mutation (n = 330)	Time to next treatment	2.7 (1.8, 4.0)	< 0.0001
	Time to treatment discontinuation	1.4 (1.0, 2.0)	0.03
	Real-world overall survival	3.2 (2.0, 5.1)	< 0.0001
No *KRAS*^{G12C} mutation (n = 938)	Time to next treatment	1.7 (1.2, 2.5)	0.02
	Time to treatment discontinuation	1.5 (1.0, 2.2)	0.007
	Real-world overall survival	1.8 (1.2, 2.8)	0.004
KRAS wildtype (n = 754)	Time to next treatment	1.7 (1.1, 2.6)	0.02
	Time to treatment discontinuation	1.4 (1.0, 2.0)	0.08
	Real-world overall survival	1.4 (0.8, 2.4)	0.3

tions and in 6 % of those with *KRAS* wildtype.

According to this analysis, *KRAS*^{G12C} and *STK11* co-mutations are associated with poor outcomes in patients treated with first-line immunotherapy. Time to next treatment (TTNT) was over four times shorter in the co-mutated group than in *KRAS*^{G12C}-mutated patients without *STK11* mutations (224 vs. 975 days; HR, 2.7; p < 0.0001; **Table**). Also, time to treatment discontinuation (TTD) was seriously reduced (172 vs. 232 days; HR, 1.4; p = 0.03), and real-world OS (rwOS) was increased by a factor of 3.2 (p < 0.0001).

Smaller differences across patients with and without co-mutations were noted for the matched no *KRAS*^{G12C} cohort and the *KRAS* wildtype cohort **(Table)**. Patients with other *KRAS* mutations who harbored *STK11* co-mutation had significantly shorter TTNT, TTD and rwOS than those without *STK11* mutations, although the adjusted HRs of TTNT and rwOS were lower than the HRs for the *KRAS*^{G12C} cohort. In the matched *KRAS* wildtype group, the differences for TTD and rwOS did not reach statistical significance. The authors summarized that these inferior outcomes indicate the high need for effective targeted and/or combination therapies in NSCLC patients with co-occurring *KRAS*^{G12C} and *STK11* mutations.

Sequencing of IO and EGFR-TKIs

Jones et al. investigated the impact of sequences with CPIs and driver-targeted TKIs on the outcomes of patients with NSCLC and oncogenic driver mutations treated within the Sarah Cannon network [9]. Overall, 230 driver-positive patients who had received CPIs were identified, with 176 of them falling into the *EGFR*-mutant category. Controls included 1,686 driver-positive and 1,352 *EGFR*-mutant patients without CPI treatment, as well as 2,868 driver-negative, CPI-treated patients and 4,308 patients without driver mutations who did not receive checkpoint inhibition.

The analysis indicated that patients with oncogene-driven NSCLC benefit from CPIs longer when they receive immunotherapy after TKIs compared to the reversed sequence. In the group with *EGFR*-mutant tumors who had EGFR TKI therapy first, time to CPI failure was significantly longer than in those with CPIs prior to EGFR TKI treatment (266 vs. 210 days; p < 0.005). However, time to EGFR TKI failure was not affected by the sequence (p = 0.55); this also applied to median overall survival for patients who received CPIs before or after EGFR TKIs (p = 0.71). Similar results were observed in the combined driver-positive cohort.

Moreover, patients with *EGFR*-positive NSCLC experienced marginally improved survival if they received CPIs independent of the sequence (2,156 vs. 1,899 days; p < 0.005). This was observed although CPI-treated patients in the *EGFR*-mutant group showed shorter time to TKI failure than those who were not administered CPI therapy. Generally, the *EGFR*-negative group had longer time to CPI failure than the *EGFR*-positive group. Again, similar results were obtained in the combined driver-positive cohort. As the authors noted, continued research is needed to identify additional clinical, therapeutic, and/or genomic biomarkers of CPI response in patients with NSCLC harboring driver aberrations. ■

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Enhancing immunosupportive mechanisms via anti-angiogenesis

Treatment with anti-angiogenic agents offers potential in the management of patients progressing on immune checkpoint inhibitors as it has been shown that excessive VEGF production can create an immunosuppressive tumor microenvironment by modulation of immune cell function and reduction of immune cell access [1-3]. This might contribute to checkpoint inhibitor resistance and prime the tumor for anti-angiogenic therapy.

VARGADO: nintedanib after chemo-immunotherapy

Anti-angiogenic treatment involving inhibition of VEGF, PDGF and FGF is assumed to enhance vessel normalization and to improve cell access to the tumor, thus favoring the restoration of an immunosupportive tumor microenvironment in the so-called angio-immunogenic switch [2]. The combination of docetaxel with the oral, triple angiokinase inhibitor nintedanib that targets VEGFR 1-3, PDGFR α/β, FGFR 1-3, and RET has been approved in many countries for the treatment of locally advanced, metastatic or locally recurrent adenocarcinoma of the lung after first-line chemotherapy. In the ongoing, prospective, non-interventional VARGADO study, nintedanib plus docetaxel is assessed under real-world conditions such as progression after chemotherapy and immunotherapy, to help inform clinical decision making. At ASCO 2021, Grohé et al. reported the initial efficacy data from Cohort C of the study that received second-line nintedanib plus docetaxel after progression on first-line chemo-immunotherapy [4]. The analysis included the first 100 patients treated in this cohort. In two thirds of cases, time since the start of first-line treatment was shorter than 9 months. Nintedanib plus docetaxel was administered according to the approved label.

After a median follow-up of 5.3 months, median PFS was 4.4 months, the overall response rate was 37.3 %, and disease control had been achieved in 67.8 % **(Table)**. Overall survival data were still immature. Drug-related AEs mainly comprised diarrhea, nausea, and fatigue. Grade ≥ 3 treatment-emergent AEs occurred in 47 %. Thirty-one percent of patients had at least on nintedanib dose reduction, and in 16 %, at least one docetaxel dose reduction was performed. Investigator-defined drug-related treatment-emergent AEs led to study drug discontinuation in 16 %. No new safety signals or unexpected toxicities emerged.

TABLE
Response rates with second-line nintedanib plus docetaxel after first-line chemo-immunotherapy

Outcome	n = 59
Objective response rate, n (%)	22 (37.3)
Complete response, n (%)	1 (1.7)
Partial response, n (%)	21 (35.6)
Stable disease, n (%)	18 (30.5)
Disease control rate, n (%)	40 (67.8)
Progressive disease, n (%)	18 (30.5)

In their conclusion, the authors noted that the initial data from Cohort C of the VARGADO study provide the first evidence that second-line nintedanib plus docetaxel has clinically meaningful efficacy and a manageable safety profile following progression on first-line chemo-immunotherapy. Recruitment and follow-up are ongoing in this cohort.

Combined VEGF/Ang2 and PD-1 inhibition

Another approach is the combination of anti-angiogenic and immunotherapeutic agents, such as the bispecific nanobody® BI 836880 that targets VEGF as well as Ang2 and the anti-PD-1 antibody ezabenlimab. BI 836880 antagonizes the immunosuppressive effects of VEGF and Ang2, thus reprogramming the tumor microenvironment [2, 5-7]. The addition of a PD-1 inhibitor drives T-cell-mediated tumor cell death. Both agents have demonstrated safety and preliminary anti-tumor activity as monotherapies in phase I studies [8, 9].

An ongoing phase Ib study aims to assess the safety and anti-tumor activity of the combination in patients with advanced or metastatic solid tumors. In the dose-escalation part, the recommended dose was defined as BI 836880 720 mg plus ezabenlimab 240 mg i. v. every 3 weeks. The cohort expansion part of the study includes seven cohorts with metastatic NSCLC, SCLC, glioblastoma, metastatic melanoma, and hepatocellular carcinoma. Cohorts A and B encompass NSCLC patients pretreated with immune checkpoint inhibitors and chemotherapy plus checkpoint inhibitors, respectively (n = 40 each). Cohort C contains SCLC patients after chemotherapy with or without immunotherapy (n = 30). Overall, 215 patients were included in the analysis presented at ASCO 2021 [10].

The combination gave rise to an overall response rate of 13 % in the total population, with 4 and 5 patients in Cohorts A and C, respectively, experiencing partial response. Stable disease was achieved in 61 % overall. All-grade treatment-related AEs emerged in 55 %, with asthenia (22 %), hypertension (19 %) and diarrhea (14 %) occurring most frequently. Immune-related AEs were observed in 16 %. The authors concluded that BI 836880 plus ezabenlimab shows preliminary antitumor activity and a manageable safety profile in a range of tumor types. ■

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Opening up new vistas for patients with SCLC

Cisplatin vs. carboplatin in LS-SCLC

Concurrent chemo-radiation with a platinum-etoposide backbone constitutes the standard of care in limited-stage small-cell lung cancer (LS-SCLC). Here, cisplatin is traditionally the preferred platinum agent. However, data on the comparative efficacy of the less toxic carboplatin in this setting are lacking. To fill this gap, Azar et al. conducted a retrospective study based on the National VA Cancer Cube database [1]. Patients with pathologically confirmed LS-SCLC who were treated with concurrent chemo-radiation containing platinum-based multiagent chemotherapy were included. Overall, the analysis comprised 1,756 individuals. Among these, 801 and 1,018 received carboplatin and cisplatin, respectively, while 63 received both. Notably, patients aged ≥ 70 were more likely to be treated with carboplatin, while in the other age groups, cisplatin prevailed.

With respect to overall survival, the Kaplan-Meier curves for the two agents were shown to be superimposable. Median OS across stages I-III was 2.24 and 2.13 years for cisplatin and carboplatin, respectively (HR, 1.040; p = 0.462). The researchers also assessed OS according to several variables. No significant differences between cisplatin and carboplatin emerged for all ECOG performance status groups (0, 1, 2), with HRs of 1.066, 0.977, and 1.216, respectively. Of course, OS was generally shorter with decreasing performance status. This also applied to age; here, younger patients (50-59 and 60-69 years) had longer OS than those aged 70 years or older. Again, however, cisplatin and carboplatin performed equally well in all groups (HRs, 1.021, 0.944, and 1.020, respectively). Similarly, TNM stage (I, II, III) did not identify any patients with greater benefits from one treatment or the other (HRs, 1.221, 1.034, and 1.020, respectively).

Accounting for all variables, the multivariable analysis showed no significant differences between cisplatin and carboplatin. As the authors concluded, concurrent chemoradiation with carboplatin-etoposide confers similar OS compared to cisplatin-etoposide in patients with LS-SCLC irrespective of performance status and age. The favorable toxicity profile of carboplatin and comparable OS benefit identify it as an acceptable option in this setting.

Advanced disease: BiTE® therapy

The delta-like ligand 3 (DLL3) is a promising target in SCLC due to its high expression in tumor tissue and minimal expression in normal cells [2]. It has been validated as a therapeutic target in previous studies [3, 4]. The DLL3-targeting, half-life–extended bispecific T-cell engager (BiTE®) tarlatamab (AMG 757) engages the patient's own T-cells to attack and eradicate DLL3-expressing cancer cells [5, 6]. At ASCO 2021, Owonikoko et al. presented updated safety, efficacy, and pharmacokinetic data from 66 patients included in the open-label, multicenter phase I study investigating tarlatamab in relapsed or refractory SCLC [7]. The study participants had received ≥ 1 line of systemic treatment and had progressed or recurred following ≥ 1 platinum-based chemotherapy.

The results support tarlatamab as the first half-life–extended BiTE® immune-oncology therapy in SCLC with an acceptable safety profile and encouraging efficacy across the dose range (i.e., 0.003-100 mg i. v. 2-weekly). Confirmed partial responses were observed in 20 % of patients, and the disease control rate was 47 %. For patients with confirmed PR, median responses lasted for a median of 8.7 months. Tarlatamab exhibited a manageable safety profile. Cytokine release syndrome (CRS) was the most common treatment-related AE (all grades, 44 %), followed by pyrexia (26 %) and fatigue (17 %). Grade ≥ 3 treatment-related AEs occurred in 27 %, which included only one CRS event (2 %). Treatment-emergent AEs resulted in discontinuation in 5 % of patients. Tarlatamab serum levels increased proportionally with the evaluated doses. Eight patients (14 %) developed treatment-emergent anti-tarlatamab binding antibodies, with no apparent impact on serum levels or AEs. The study is ongoing.

Multiomic characterization

Based on the dominant expression of four lineage-defining transcription factors (*ASCL1*, *NEUROD1*, *YAP1*, *POU2F3*), SCLC has been divided into four subtypes (SCLC-A/N/Y/P) [8]. Puri et al. conducted comprehensive molecular profiling of 437 small-cell lung neuroendocrine tumors (including 7.3 % high-grade neuroendocrine lung carcinomas) using next-generation DNA sequencing (592-gene panel), RNA sequencing (whole transcriptome) and immunohistochemistry [9]. Tumors were stratified

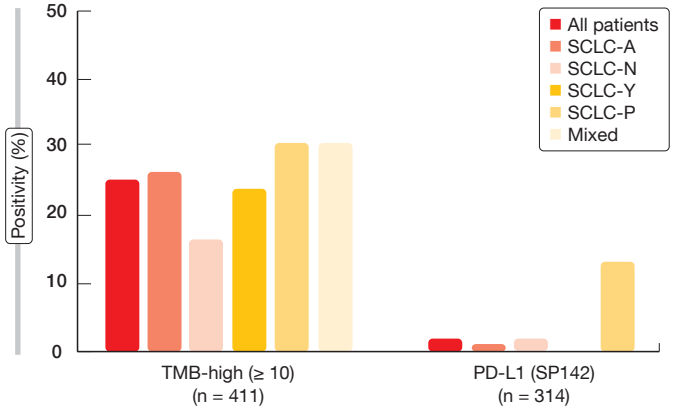

Figure: Clinically relevant biomarkers of response to immunotherapy across transcriptionally defined SCLC subtypes

into five subgroups (SCLC-A/N/Y/P and mixed) based on the relative expression of the four transcription factors.

This analysis represents the largest real-world dataset of human SCLC tumors profiled by next generation DNA and whole transcriptome sequencing. It revealed differential expression of immune genes and predictive biomarkers across the subtypes. For instance, the SCLC-Y subtype showed the highest median expression of immune-related signatures and immune-related cell types. The highest expression of *SLFN11* and *SSTR2* genes was observed in the SCLC-N subtype, while *MYC* gene expression was highest in SCLC-P. This subtype also most frequently demonstrated high tumor mutational burden, along with the mixed group, and showed significantly increased PD-L1 expression according to the SP142 assay (13 %; p = 0.0046; **Figure**). CNS metastases mainly originated in the neuroendocrine-high subtypes (SCLC-A and SCLC-N). The *RB1* mutation frequency was highest in the ASCL1 group (79.2 %) and lowest in the YAP1 group (49.4 %). According to the researchers, differential expression of genes and biomarkers might inform therapeutic vulnerabilities for rational and personalized treatment approaches in SCLC. ■

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Interview: Donald Harvey, PharmD, Emory University School of Medicine, Atlanta, USA

Resistance is all too often looming with targeted therapies

In which ways is resistance being tackled in the setting of targeted agents?
Resistance is the biggest challenge across the landscape of different compounds such as the new RET or MET inhibitors. I think it is promising to look at the story of *EGFR*-activating mutations, as initially we had gefitinib and erlotinib but were unaware of how they actually worked until the mutation data evolved. Subsequently, more potent compounds were created that continue to extend the time of patients on these treatments through improved medicinal chemistry and superior target binding. For the newer agents such as $KRAS^{G12C}$ inhibitors, we are seeing good results, but resistance is real and already emerging. Thus, strategies to prevent resistance from the outset are needed, such as engineering agents that can inhibit both likely resistance mechanisms and the primary target. My hope is that we might be able to head this problem off earlier rather than later by exploring circulating tumor cells and blood-based markers of potential resistance development in a given patient. Much effort and technology are being invested trying to improve the outcomes of these patients across different platforms of science and drug discovery.


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Donald Harvey, PharmD,
Emory University School of Medicine,
Atlanta, USA

How can the design of clinical trials in the lung cancer setting be optimized to better meet the demands of modern drug development?
We need to be able to identify patients early and effectively through broad-based genomic platforms that ideally include data sharing. These days, next generation sequencing is performed in all lung cancer patients at many centers, but the clinical picture of the individual patient might not be suitable for enrollment in a trial investigating a new agent. Therefore, data sharing and having rapid opening opportunities for trials is important, as well as getting trials out into the community. Many times, patients are identified in the community but are unable to come to larger centers for treatment on trials.

With respect to the scientific design of trials, the tight link between molecular biology and the drug allows us to work with lower numbers of patients and observations. When patients are preselected to respond, the development of that drug can be accelerated in a fashion that allows for phase II or other early data to provide the basis for approval. Regarding execution of a trial, many sites are necessary to identify patients worldwide if they represent a rare population or if the genetic abnormality shows low penetrance. Some of the recent successful drug development stories are based on worldwide enrollment. Spreading that out as widely as possible will be critical to rapid trial completion and earlier agent access. ■

ASCO Congresses

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Expert interviews at ASCO 2021

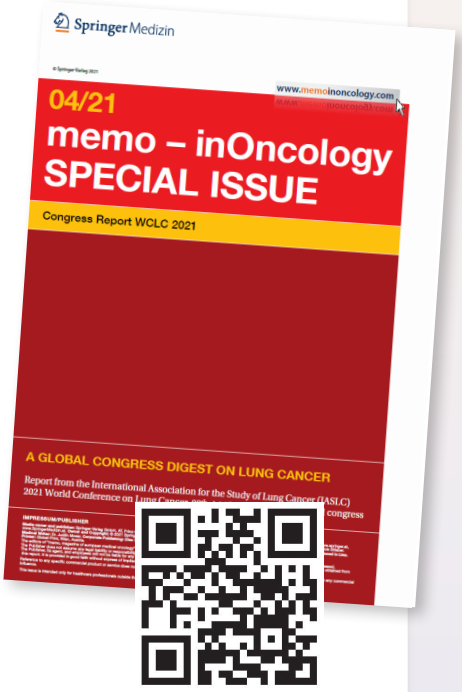
Martin Reck compares the combination of novel immune checkpoint inhibitors with other drug classes to monotherapy in terms of efficacy and tolerability, discusses the role of biomarkers and the tumor microenvironment in terms of treatment decision and focuses on the potential predictive value of immune-related adverse events.

David Cooke talks about health equity and health disparities relating to lung cancer management in the western world. He explains which factors based on ethnicity are likely to affect outcomes of lung cancer patients and how health disparities might be tackled in the long run at the public health level.

Donald Harvey discusses lung cancer from the point of view of clinical pharmacology, targets in the area of antibody-drug conjugates, the role of proteolysis targeting chimeras (PROTACs) in the treatment landscape, highlights mechanisms of resistance to small molecule inhibitors and draws attention to clinical trial design to better meet the demands of modern drug development.

Luis Paz-Ares explains which notable developments are taking place in the field of small-cell lung cancer with respect to new targets and targeted agents, how chemotherapeutic standards will change in the management of patients with small-cell lung cancer and highlights the most relevant findings presented at ASCO 2021 in terms of targeted therapies.

Ferdinandos Skoulidis summarizes why the development of KRASG12C-targeted therapies failed in the past, relates to new developments in the field of KRASG12C inhibition with a focus on sotorasib and discusses the impact of co-mutations on personalized anticancer therapy.



Forthcoming Special Issue

This special issue will be offering a synopsis from the ESMO 2021 that will be held in September 2021. The report promises to make for stimulating reading, as the ESMO Congress itself draws on the input from a number of pvartner organizations, representing a multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

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