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ESMO Lung Cancer 2022

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

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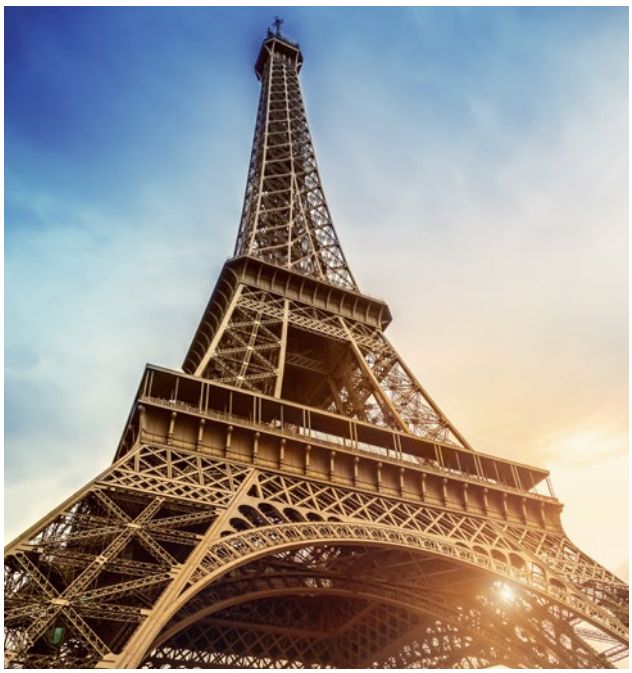
Table of Contents



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Preface

Dear Colleagues,

At the ESMO Congress held in Paris, France, and virtually from 9th to 13th September 2022, practice-changing data and high-quality education attracted more than 29,300 participants from over 150 countries. The 1,912 abstracts reported at the conference included 76 late-breaking abstracts, and 11 abstracts were selected for presidential symposia to discuss the most exciting updates across different tumor types including therapeutic innovations, translational research, patient advocacy, public policy, and many more.

This issue of memo inOncology summarizes some of the lung cancer highlights presented at the ESMO 2022 Congress. In the (neo)adjuvant setting, the data underscore the importance of patient selection and have confirmed innovative treatment approaches while demonstrating the potential of new combinations. An entire chapter is devoted to new ways to further improve patient outcomes in the setting of metastatic lung cancer by targeting $KRAS^{G12C}$, EGFR, HER2, and angiogenesis in the first and later lines. Among others, the results suggest a new second-line standard option for patients with advanced *$KRAS^{G12C}$*-mutated NSCLC and a potential chemotherapy-sparing targeted strategy in the treatment of patients with *EGFR*-mutant NSCLC harboring *MET* amplifications. Updates on immunotherapy-based approaches show sustained outcome improvement with single agents or combination regimens. Immune checkpoint inhibition also offers an effective first-line alternative in the important understudied patient population with poor performance status who have multiple comorbidities and poor tolerance of treatment.

Furthermore, data presented at ESMO dealt with the close association between air pollution and increased lung cancer risk, indicating a significant association between the exposure to atmospheric particulate matter with a diameter ≤ 2.5 µm and *EGFR*-mutant lung cancer incidence across the globe. Insights were also obtained with respect to the role of inflammation in the promotion of a cancer-stem-cell–like state. Last but not least, the benefits of lung cancer mass screening are discussed on the basis of a study conducted in China.

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Once again, the ESMO meeting was a place to build strong, meaningful academic relationships with colleagues and peers in the field of lung cancer while concomitantly enabling an environment for sharing clinical cases and debates aiming at providing better care for patients.

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Treatment benefits and outcome determinants in (neo)adjuvant trials

ADAURA: study update

The adjuvant use of the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib is being explored in the phase III ADAURA study that includes almost 700 patients with completely resected stage IB, II, and IIIA, *EGFR*-mutant non-small-cell lung cancer (NSCLC), with or without adjuvant chemotherapy. The primary analysis has revealed benefits of osimertinib compared to placebo with respect to disease-free survival (DFS) in patients with stage II/IIIA disease (36-month DFS rates, 78 % vs. 28 %; HR, 0.17; $p < 0.001$) and in the overall population (36-month DFS rates, 79 % vs. 40 %; HR, 0.20; $p < 0.001$) [1, 2]. At ESMO 2022, Tsuboi presented an updated DFS analysis at the protocol-specified maturity of 50 % as well as other findings after 2 more years of follow-up [3]. All patients had had the opportunity to complete 3 years of planned study treatment.

These updated data corroborated the previous results. For the primary endpoint, the analysis yielded median DFS of 65.8 vs. 21.9 months in the stage II/IIIA population, with 48-month DFS rates of 70 % vs. 29 % **(Figure 1)**. This translated into a 77 % risk reduction (HR, 0.23). In the overall population, median DFS was 65.8 vs. 28.1 months, and 73 % vs. 38 % of patients were disease-free at 48 months (HR, 0.27). DFS benefits with osimertinib were observed across all predefined subgroups. In the groups with and without adjuvant chemotherapy, the HRs

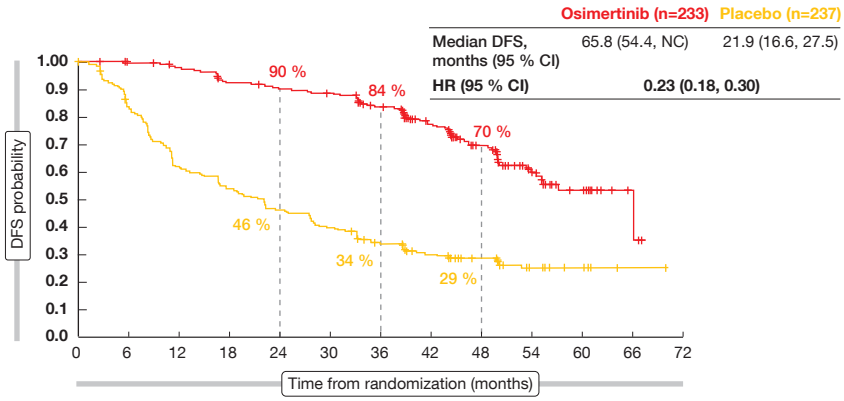

Figure 1: Updated disease-free survival results obtained with adjuvant osimertinib vs. placebo in the ADAURA study

for DFS were 0.29 and 0.36, respectively. During the study, the patients had been restaged according to the AJCC/IUCC 8th edition staging manual; however, the proportions of stages according to the 7th and 8th editions were similar, and the DFS results were consistent across all stages.

The authors also reported a prespecified exploratory analysis of recurrence patterns in the overall population. Fewer patients treated in the experimental arm had disease recurrence (27 % vs. 60 %), as osimertinib treatment reduced the risk of both locoregional and distant relapses. The most common first sites of recurrence were identical in the two arms, with lower rates for osimertinib in the lung (12 % vs. 26 %), the lymph nodes (6 % vs. 17 %), and the CNS (6 % vs. 11 %). Updated results on DFS in the CNS in 63 patients with stage II/IIIA disease showed that 14 % were on osimertinib treatment at the time of CNS recurrence, vs. 71 % in the placebo group. Median CNS DFS had not been reached yet in either arm, and the 48-month rates were 90 % vs. 75 %. Here, the osimertinib-mediated relative risk reduction was as high as 76 % (HR, 0.24), with the cumulative incidence of CNS relapses being consistently lower in the experimental arm than in the placebo arm. The estimated probability of observing CNS recurrence at 36 months was 2 % vs. 13 %. No new safety concerns emerged with the extended treatment duration. In their entirety, the updated results reinforce adjuvant osimertinib as the standard of care for patients with *EGFR*-mutant, stage IB-IIIA NSCLC after complete tumor resection, with or without adjuvant chemotherapy.

ctDNA monitoring after resection of *EGFR*-mutant NSCLC

Personalization of adjuvant strategies such as anti-EGFR treatment with osimertinib requires the selection of patients who are most likely to benefit from adjuvant EGFR TKI therapy, with the aim to reduce costs and avoid unnecessary side effects as well as the psychological burden of long-term treatment. Circulating tumor DNA (ctDNA) provides a potentially valuable biomarker for early diagnosis, prognostic stratification, detection of minimal residual disease (MRD), and recurrence. Ahn et al. investigated the role of longitudinal monitoring of ctDNA in 278 patients with curatively resected stage IA-IIIA, *EGFR*-mutant NSCLC. The radiological follow-up was accompanied by serial ctDNA monitoring using droplet digital PCR. Samples were taken preoperatively, 4 weeks after surgery and in increasing intervals for 5 years (every 3 months in year 1, every 4 months in year 2, every 6 months in year 3 and annually thereafter) or until clinically definitive recurrence.

At the time of the analysis reported at ESMO 2022, the median follow-up was 62.0 months [4]. Baseline ctDNA was detected in 67 patients (24.1 %). ctDNA detection rates trended to increase with the disease stage (IA, 23.4 %; IB, 17.6 %; IIA, 17.9 %; IIB, 50.0 %; IIIA, 42.3 %). The same observation was made for baseline ctDNA copy numbers, with the difference being significant ($p < 0.0001$). Overall, 51 of the 67 patients who had baseline ctDNA showed ctDNA clearance 4 weeks after surgery (76.1 %). This was fairly comparable across the stages. With respect to the type of *EGFR* mutation, the analysis did not reveal any differences between exon 19 deletion and L858R mutation regarding ctDNA detection rates (24 % vs. 24.3 %) or clearance rates (75 % vs. 77.8 %).

Relapses occurred in 28.1 %. The 3-year DFS rate was highest in patients with ctDNA negativity at baseline (83.3 %), while it was slightly lower for those with ctDNA positivity but MRD negativity 4 weeks after surgery (78.0 %) and considerably lower for those who were positive for both markers (50.0 %). These differences were significant ($p = 0.02$). According to a multivariate analysis including various clinicopathologic variables, the ctDNA group remained an independent determinant of DFS regardless of stage (HR, 1.27; $p = 0.03$). These results suggest that baseline ctDNA positivity and MRD positivity are associated with poor DFS in curatively resected stage IA-IIIA, *EGFR*-mutant NSCLC.

CheckMate 816: significance of pathological features

The randomized phase III CheckMate 816 study investigated neoadjuvant nivolumab plus platinum-doublet chemotherapy compared to chemotherapy alone in 358 patients with newly diagnosed, resectable, stage IB(≥ 4 cm)-IIIA NSCLC. Surgery was performed within 6 weeks post-treatment and was followed by optional adjuvant chemotherapy with or without radiotherapy. Compared to chemotherapy, the combination significantly improved event-free survival (EFS) and pathologic complete response (pCR) [5]. In an additional analysis, EFS was improved with both strategies in patients with pCR or major pathologic response (MPR) in the primary tumor relative to patients without [6]. Here, lower percentages of residual viable tumor (% RVT) were associated with improved EFS in the experimental arm. A post-hoc analysis relating to the results in patients with or without pathologic evidence of lymph node involvement from CheckMate 816 was presented at ESMO 2022 [7].

The addition of nivolumab to chemotherapy led to similar EFS and pCR benefits in patients with and without lymph node involvement **(Table 1)**. Closer inspection of the group with lymph node involvement who had received the combination showed that

TABLE 1 **Efficacy of nivolumab plus chemotherapy vs. chemotherapy only in patients with or without pathologic evidence of lymph node involvement**

Outcome	Patients with lymph node involvement		Patients without lymph node involvement	
	Nivolumab + chemotherapy (n = 68)	Chemotherapy (n = 74)	Nivolumab + chemotherapy (n = 72)	Chemotherapy (n = 51)
Median EFS, months	31.6	22.7	Not reached	Not reached
	HR, 0.69		HR, 0.74	
12-month EFS rates, %	80	70	87	76
24-month EFS rates, %	62	47	77	64
pCR rates, %	19	1	40	6

EFS, event-free survival; pCR, pathological complete response

19 % had achieved 0 % RVT in both the primary tumor and the lymph nodes, which equals pCR. This cohort derived the best 24-month EFS rate of 92 %, followed by 76 % in those who had 0 % RVT in either the primary tumor or the lymph nodes but not in both. Not surprisingly, the lowest rate (49 %) resulted in patients with residual viable tumor (> 0 % RVT) in both the primary site and the nodes. This observation adds to the growing body of evidence demonstrating that pathologic response might predict long-term outcomes in resectable NSCLC. However, clinically relevant % RVT thresholds beyond pCR warrant further investigation.

The assessment of the % RVT was achieved by pathologic recognition of tumor regression, i.e., the area occupied by the tumor prior to immune-mediated clearance [8, 9]. Nivolumab plus chemotherapy led to lower % RVT and higher % regression compared to chemotherapy only, while the extent of necrosis did not differ between the treatment arms. According to a time-dependent ROC curve analysis, % regression and % RVT in the primary tumor predicted EFS at 2 years in a similar manner in the experimental arm. Taken together, these findings further support the neoadjuvant use of nivolumab plus chemotherapy as a novel treatment option for patients with resectable NSCLC irrespective of lymph node involvement.

Health-related quality of life in CheckMate 816

Another piece of evidence underscoring the benefits obtained with the CheckMate 816 regimen is the health-related quality of life (HRQoL) analysis reported by Felip et al. [10]. Prespecified patient-reported outcome exploratory endpoints in CheckMate 816 were investigated using the EQ-5D visual analog scale (VAS) and the EQ-5D health status utility index (EQ-5D UI). Assessments were performed before the start of the neoadjuvant treatment, before cycles 2 and 3, at post-neoadjuvant visit 1 (approximately 30 days after the last dose) and post-neoadjuvant visit 2 (approximately 70 days after the first post-neoadjuvant visit).

The EQ-5D VAS and UI scores from baseline to post-neoadjuvant visit 1 in all randomized patients yielded no differences across the treatment arms, with scores being similar to those obtained in the UK population norm. EQ-5D VAS and UI scores during the neoadjuvant period and post-surgery (i.e., until post-neoadjuvant visit 2) showed slight declines after surgery, although these were similar in both arms and are consistent with previous reports [11-13]. No notable differences in EQ-5D VAS and UI scores were seen between the treatment arms across patient subgroups in the post-operative population. Overall, HRQoL was preserved from baseline during the neoadjuvant treatment period with nivolumab plus chemotherapy similar to chemotherapy alone, and the combination did not impact post-operative patient-reported outcomes compared to chemotherapy only.

NEOpredict-Lung: nivolumab plus relatlimab

The randomized, phase II NEOpredict-Lung trial examined the combined neoadjuvant administration of nivolumab and relatlimab on days 1 and 15 in patients with stage IB, II or IIIA NSCLC for whom curative resectability had been established by the multidisciplinary lung cancer board. Relatlimab is a monoclonal antibody targeting the immune checkpoint LAG-3; the efficacy of nivolumab plus relatlimab in melanoma has been demonstrated by the RELATIVITY-047 trial [14]. In the control arm of the NEOpredict-Lung study, nivolumab monotherapy was administered on day 1 and 15. Each treatment group contained 30 patients. After surgery, the patients received standard-of-care adjuvant therapy. Schuler et al. reported first results for the primary endpoint, which was feasibility of curatively intended surgery within 43 days, and other outcomes [15].

As the analysis showed, preoperative combined immune-checkpoint inhibitor therapy with 2 courses of nivolumab and relatlimab is safe and feasible. Treatment-related adverse events (TRAEs) were mostly grade 1 and 2 and consistent with the known profiles **(Table 2)**. No patient experienced delay

TABLE 2 **NEOpredict-Lung: treatment-related adverse events observed with nivolumab/relatlimab vs. nivolumab**

	Nivolumab + relatlimab		Nivolumab	
	All	Grade ≥ 3	All	Grade ≥ 3
Anemia	-	-	2 (7 %)	-
Atrial fibrillation	-	-	1 (3 %)	1 (3 %)
Hyperthyroidism	4 (13 %)	-	5 (17 %)	1 (3 %)
Hypothyroidism	3 (10 %)	-	2 (7 %)	-
Gastrointestinal	2 (7 %)	-	1 (3 %)	-
Hepatic	1 (3 %)	1 (3 %)	1 (3 %)	1 (3 %)
Proteinuria	-	-	1 (3 %)	-
Pneumonitis	2 (7 %)	-	-	-
Chills/fever	-	-	2 (3 %)	-
Rash	-	-	1 (3 %)	-

of surgery due to toxicity, and all patients in both arms were able to undergo surgery within 43 days. Overall response rates according to RECIST 1.1 were 27 % and 10 % for the combination and nivolumab monotherapy, respectively. Thirty-one patients received sequential FDG PET/CT at baseline and prior to surgery at one institution. This allowed for the assessment of metabolic response, which was 38 % in both arms. Complete and major pathological responses occurred in 30 % vs. 27 %. R0 resection was performed in 97 % vs. 100 %. At 12 months, 100 % vs. 92 % of patients were alive, and 91 % vs. 92 % were disease-free.

All PD-L1 expression groups experienced histopathological responses, although a trend towards deeper remissions emerged in patients with PD-L1–positive tumors. Also, complete remissions were restricted to this group. Patients who had ≤ 50 % vital tumor cells in their resected tissue tended to show increased effector T cell counts in the peripheral blood. Comprehensive correlative studies and biomarker analyses are ongoing. In addition, the protocol has been amended to add a third treatment arm that explores a higher dose of relatlimab for increased LAG-3 target occupancy.

Ipi/nivo in addition to CRT: INCREASE

A segment of patients with stage III NSCLC who have high T-stage and low N-stage (e.g., superior sulcus tumors) is borderline resectable and might become resectable after induction with chemoradiotherapy (CRT). Based on the assumption that the combination of pre-operative CRT with dual checkpoint inhibition could enhance pathological and immunological response rates through activation of antigen-presenting cells and effector T cells, the single-arm, prospective, phase II INCREASE study assessed the following regimen: in patients with cT3-4 N0-2 M0 NSCLC eligible for post-induction resection, nivolumab plus ipilimumab was administered on day 1 of CRT, and nivolumab alone was administered on day 22. The patients underwent surgery 6 weeks after the end of treatment. Pathological responses (i.e., pCR, MPR) and safety constituted the primary endpoint. Twenty-seven individuals received induction therapy, and 24 proceeded to surgery.

In the group of operated patients, the treatment resulted in substantial responses, with pCR and MPR rates of 63 % and 79 %, respectively [16]. Compared to the historical reference of 30 %, the difference for pCR was significant ($p < 0.001$). In terms of radiological response, 12.5 % and 87.5 % of the resected population achieved partial remissions (PR) and stable disease (SD), respectively. There were no differences between the groups who had achieved pCR vs. MPR regarding PR (13 % vs. 11 %) or SD (87 % vs. 89 %).

The toxicity rates were acceptable, with grade 3/4 TRAEs in 67 % and grade 3/4 immune-related AEs in 19 %. No patient failed to undergo surgery or died due to TRAEs. Among immune-related AEs, dermatitis was observed most commonly (any grade, 41 %), followed by thyroid disorders (33 %), pneumonitis (11 %), and hepatitis (7 %). According to a translational analysis, induction treatment led to higher levels of CD8-positive effector T cells in the peripheral blood. The CD39-positive T cell subset mainly increased in patients who had achieved pCR. A comparison with historical controls (i.e. matched patients who underwent CRT and surgery without immunotherapy) showed increased CD8-positive T cell proliferation in tumor-draining lymph nodes.

PEARLS/KEYNOTE-091 results according to PD-L1 expression

In the randomized, triple-blind, phase III PEARLS/KEYNOTE-091 study, adjuvant pembrolizumab for ≤ 18 administrations (n = 590) was tested against placebo (n = 587) in patients with confirmed stage IB (T ≥ 4 cm), II, or IIIA NSCLC after complete surgical resection with negative margins (i.e., R0 resection). Adjuvant chemotherapy for a maximum of 4 cycles was optional. The dual primary endpoints included DFS in the overall population and in the group with PD-L1 TPS > 50 %. At the time of the second interim analysis after a median follow-up of 35.6 months, DFS prolongation with pembrolizumab compared to placebo was clinically meaningful and statistically significant in the overall population (HR, 0.76; p = 0.0014) but, surprisingly, not in the population with PD-L1 expression > 50 % (HR, 0.82; p = 0.14) [17]. In search of an explana-

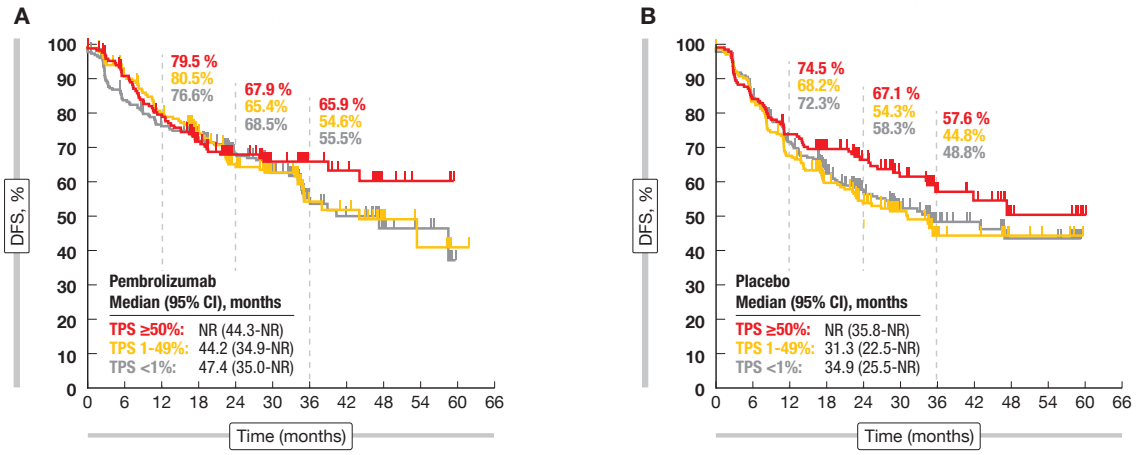

Figure 2: Disease-free survival performance of pembrolizumab (left) and placebo (right) according to the three PD-L1 categories in PEARLS/KEYNOTE-091

tion for this discrepancy, Peters et al. evaluated the trial outcomes according to PD-L1 expression status [18].

The baseline characteristics were generally similar across the overall population and the PD-L1 ≥ 50 % population and were also balanced between the treatment arms within both groups. All-cause AEs as well as immune-mediated AEs and infusion reactions were similar for the overall and PD-L1-high populations, which also applied to treatment exposure. The DFS analysis showed significant risk reductions with pembrolizumab vs. placebo for the groups with TPS 1-49 % (HR, 0.67) and TPS < 1 % (HR, 0.78). As expected, median and long-term DFS estimates were numerically improved with pembrolizumab in the TPS ≥ 50 % population *versus* the TPS 1-49 % and < 1 % groups; however, the difference within the TPS ≥ 50 % group was offset by the fact that the placebo arm also performed better than the placebo arms in the other groups **(Figure 2)**. Median DFS had not been reached yet in either arm of the TPS ≥ 50 % population. Therefore, the absence of a statistically significant DFS benefit in this group is likely to have resulted from placebo overperformance.

Overall, these data from the PEARLS/KEYNOTE-091 trial confirm the benefit of pembrolizumab in patients with completely resected stage IB-IIIA NSCLC and, if recommended, prior adjuvant chemotherapy, regardless of PD-L1 expression. DFS in the TPS ≥ 50 % population will be tested again at the next interim analysis.

No benefits of adjuvant canakinumab

Negative results were obtained for the adjuvant use of the anti-IL-1β antibody canakinumab in the placebo-controlled phase III CANOPY-A trial [19]. IL-1β is a key mediator of inflammation, and canakinumab has been approved in many countries for the management of inflammatory conditions. In the phase III CANTOS study evaluating the role of canakinumab in cardiovascular disease, an exploratory analysis had shown reductions in the incidence and mortality of NSCLC [20], which led to the launch of CANOPY-A. Almost 1,400 patients with completely resected, stage IIA-IIIA and IIIB (T > 5 cm, N2) NSCLC who had received cisplatin-based chemotherapy and/or radiation therapy participated in the trial.

DFS, which was the primary endpoint, did not differ between the canakinumab-treated arm and the placebo arm (35.0 vs. 29.7 months; HR, 0.94; p = 0.258) [19]. The subgroup analysis based on demographics, disease characteristics, and biomarkers of interest did not show any meaningful differences across the treatment arms. Likewise, lung-cancer–specific survival was similar for canakinumab and placebo (HR, 0.90). OS was not formally tested due to the lack of significance regarding DFS. No new safety concerns arose; infections constituted the most common AEs of special interest and were reported with comparable incidences. Also, the assessment yielded similar rates of AEs, serious AEs, and fatal serious AEs.

Exploratory biomarker data will continue to be analyzed, including tumor molecular profiling and longitudinal analyses of circulating inflammatory markers. The collective data gained throughout the CANOPY study program that further includes a neoadjuvant trial and two studies conducted in the advanced disease setting will continue to elucidate the role of IL-1β in NSCLC and inform ongoing research. ■

REFERENCES

1 Wu YL et al., Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med 2020; 383(18): 1711-1723
2 Herbst R et al., Osimertinib as adjuvant therapy in patients with stage IB–IIIA EGFR mutation positive (EGFRm) NSCLC after complete tumor resection: ADAURA. J Clin Oncol 2020; 38: 18_suppl.LBA5
3 Tsuboi M et al., Osimertinib as adjuvant therapy in patients with resected EGFRm stage IB-IIIA NSCLC: updated results from ADAURA. ESMO 2022, LBA47
4 Ahn MJ et al., Longitudinal monitoring of circulating tumor DNA from plasma in patients with curative resected stage IA-IIIA EGFR mutant non-small cell lung cancer. ESMO 2022, abstract 933MO
5 Forde PM et al., Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 2022; 386(21): 1973-1985
6 Provencio-Pulla M et al., Neoadjuvant nivolumab + platinum-doublet chemotherapy versus chemo for resectable (IB–IIIA) non-small cell lung cancer: Association of pathological regression with event-free survival in CheckMate 816. J Clin Oncol 2022; 40: 17_suppl.LBA8511
7 Stein Deutsch J et al., Analysis of pathological features and efficacy outcomes with neoadjuvant nivolumab plus platinum-doublet chemotherapy for resectable non-small cell lung cancer in CheckMate 816. ESMO 2022, abstract LBA50
8 Cottrell TR et al., Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). Ann Oncol 2018; 29(8): 1853-1860
9 Stein JE et al., Pan-tumor pathologic scoring of response to PD-(L)1 blockade. Clin Cancer Res 2020; 26(3): 545-551
10 Felip E et al., Nivolumab plus platinum-doublet chemotherapy versus chemotherapy as neoadjuvant treatment for resectable non-small cell lung cancer: health-related quality of life outcomes from CheckMate 816. ESMO 2022, abstract 932MO
11 Balduyck B et al., Quality of life evolution after lung cancer surgery: a prospective study in 100 patients. Lung Cancer 2007; 56(3): 423-431
12 Ichimura H et al., Preoperative predictors of restoration in quality of life after surgery for lung cancer. Thoracic Cancer 2021; 12(6): 835-844
13 Poghosyan H et al., Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: a systematic review. Lung Cancer 2013; 81(1): 11-26
14 Tawbi HA et al., Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med 2022; 386: 24-34
15 Schuler M et al., A randomized phase II study of preoperative nivolumab plus relatlimab over nivolumab in patients with resectable non-small-cell lung cancer. ESMO 2022, abstract LBA37
16 Bahce I et al., Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable lung cancer: the INCREASE trial. ESMO 2022, abstract 950O
17 O'Brien M et al., Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol 2022; doi.org/10.1016/ S1470-2045(22)00518-6
18 Peters S et al., PD-L1 expression and outcomes of pembrolizumab and placebo in completely resected stage IB-IIIA NSCLC: subgroup analysis of PEARLS/KEYNOTE-091. ESMO 2022, abstract 930MO
19 Garon EB et al., CANOPY-A: phase III study of canakinumab as adjuvant therapy in patients with completely resected non-small cell lung cancer. ESMO 2022, LBA49
20 Ridker PM et al., Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet 2017; 390(10105): 1833-1842

Targeted approaches in the first and later lines: KRAS^{G12C}, EGFR, HER2 & angiogenesis

The first-in-class, oral, irreversible KRAS^{G12C} inhibitor sotorasib has given rise to durable clinical benefits in patients with advanced *KRAS*^{G12C}-mutated NSCLC in the phase II CodeBreak 100 trial, with an objective response rate (ORR) and median progression-free survival (PFS) of 37.1 % and 6.8 months, respectively [1]. Median overall survival (OS) was 12.5 months. CodeBreaK 200, the first phase III study for a KRAS^{G12C} inhibitor, compared sotorasib 960 mg/d (n = 171) with docetaxel 75 mg/m² Q3W (n = 174) in patients with *KRAS*^{G12C}-mutated, locally advanced or metastatic NSCLC after ≥ 1 treatment including both platinum-based chemotherapy and checkpoint inhibition. Crossover from docetaxel to sotorasib was permitted after a protocol amendment.

Thirty-four percent of patients had a history of CNS involvement, while active brain metastases were not permitted. The majority had received ≥ 2 lines of therapy. PFS by blinded independent central review constituted the primary endpoint. Johnson et al. presented the primary analysis at the ESMO 2022 Congress [2].

Sotorasib as second-line standard

CodeBreaK 200 met its primary endpoint, with median PFS of 5.6 vs. 4.5 months (HR, 0.66; p = 0.002; **Figure 1**) after a follow-up of 17.7 months. The PFS rates at 12 months were more than double with sotorasib than with docetaxel (24.8 % vs. 10.1 %). All subgroups derived PFS benefits; an intriguing signal was the HR of 0.53 in patients with a history of CNS involvement, which hints at the potential of sotorasib to exert disease control in the CNS.

Likewise, a significantly higher proportion of patients in the experimental arm developed responses (28.1 % vs. 13.2 %; p < 0.001) and disease control (82.5 % vs. 60.3 %). Tumor shrinkage was achieved in 80.4 % and 62.8 % of patients, respectively. Sotorasib showed an association with both shorter time to response (1.4 vs. 2.8 months) and longer duration of response (DoR; 8.6 vs. 6.8 months). For OS, the analysis revealed no difference between the regimens (10.6 vs. 11.3 months; HR, 1.01; p = 0.53). However, the CodeBreaK 200 study was not powered to estimate OS, and 34 % of patients treated with docetaxel went on to receive subsequent KRAS^{G12C} inhibition, which included crossover.

Sotorasib was well tolerated. While the most common grade ≥ 3 treatment-related AEs (TRAEs) observed with the KRAS^{G12C} inhibitor included diarrhea and transaminase elevations, this was neutropenia, fatigue, and febrile neutropenia for docetaxel. Patients in the experimental arm experienced fewer grade ≥ 3 TRAEs (33.1 % vs. 40.4 %) and fewer serious TRAEs (10.7 % vs. 22.5 %) despite longer treatment (20 vs. 12 weeks).

The patient-reported outcomes analysis showed that the changes in global health status, physical functioning, and dyspnea from baseline to week 12 favored sotorasib. Compared with docetaxel, the targeted treatment significantly delayed the time to deterioration in global health status (HR, 0.69), physical functioning (HR, 0.69), and dyspnea as well as cough (HRs, 0.63 and 0.55, respectively). For chest pain, there was a trend in favor of sotorasib. Overall, these results support sotorasib as a new second-line standard option for patients with advanced *KRAS*^{G12C}-mutated NSCLC, and reinforce the importance of NGS testing for *KRAS*^{G12C} mutations.

APPLE: switch to osimertinib based on T790M monitoring

EGFR T790M mutations have been established as a strong predictive marker for the efficacy of the third-generation EGFR TKI osimertinib, with liquid biopsy representing a useful tool for genomic profiling. The randomized, phase II APPLE trial was designed to prospectively validate the benefit of dynamic treatment decisions based on longitudinal T790M assessment using liquid biopsy in patients with EGFR-TKI–naïve, advanced NSCLC harboring the common *EGFR* mutations deletion 19 and L858R mutation. First-line treatment was administered in 3 arms: the exploratory arm A received osimertinib until progression, while arms B (n = 52) and C (n = 51) were treated with gefitinib followed by osimertinib. Liquid biopsy analyses were conducted centrally once monthly in all arms, although they were only used for treatment decisions in arm B. In this arm, either detection of the T790M mutation or radiological progression by RECIST 1.1 prompted the switch from gefitinib to osimertinib, whereas in arm C, gefitinib was switched to osimertinib based on radiological progression alone. At ESMO 2022, Remon et al. presented the results obtained in arms B vs. C.

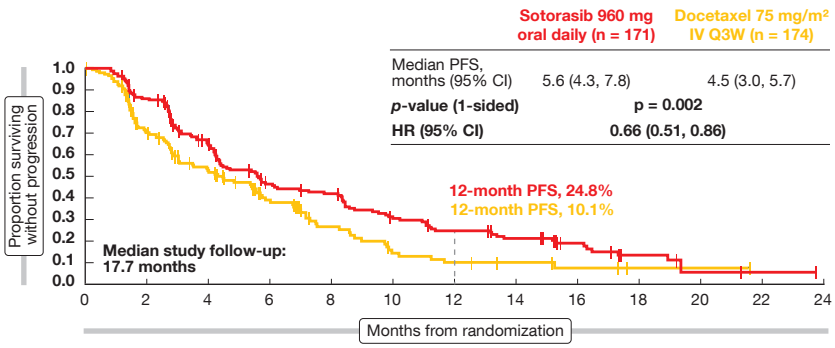

Figure 1: Primary endpoint of CodeBreaK 200: superior progression-free survival with sotorasib vs. docetaxel

TABLE 1 Outcomes for gefitinib followed by osimertinib based on ctDNA monitoring and radiological progression (Arm B) or radiological progression only (Arm C)

	Arm B		Arm C
Response rate on gefitinib, %	53.2		56.8
Median progression-free survival on gefitinib, months	10.7		9.8
Response rate on osimertinib, %	65.6		58.8
	p = 0.5692		
	ctDNA 87.5	RECIST 58.3	Not applicable
Median treatment duration of gefitinib + osimertinib, weeks	78.6 (range, 3.6-159.6)		67.1 (range, 1.1-191.7)

According to the results reported at ESMO 2022, 68 % and 77 % of patients in arms B and C, respectively, switched from gefitinib to osimertinib [3]. Serial monitoring of the T790M status identified 17 % of patients in arm B who had molecular progression before RECIST disease progression, thus giving rise to earlier treatment switches. Median time to molecular progression was almost 9 months. With respect to the PFS rates at 18 months on osimertinib treatment that were defined as the primary endpoint, the analysis showed a numerical advantage in arm B over arm C (67.2 % vs. 53.5 %; HR, 0.80; p = 0.22). Moreover, the patients experienced clinically meaningful PFS (22 vs. 20.2 months) and OS (not reached vs. 42.8 months). At 18 months, 87 % vs. 77 % of patients were alive.

Response rates on osimertinib amounted to 65.6 % vs. 58.8 % in arms B vs. C, with longer median treatment duration in the experimental arm **(Table 1)**. Within arm B, the response rate for patients who were switched based on ctDNA was higher than that for the group switched due to radiological progression. According to an exploratory analysis, ctDNA clearance of *EGFR* mutations on gefitinib treatment at weeks 4, 8 and 12 was an early predictor of longer PFS. As the authors pointed out, serial monitoring of the T790M status by ctDNA was shown to be feasible for informing treatment decisions in the setting of *EGFR*-mutant advanced NSCLC.

Molecular profiling of resistance mutations in ELIOS

In the first-line treatment setting of advanced *EGFR*-mutant NSCLC, osimertinib is a preferred option, although resistance eventually develops [4, 5]. Available tissue-based data on alterations at the time of first-line osimertinib resistance are limited. Therefore, the phase II ELIOS study characterized resistance mechanisms to first-line therapy with osimertinib in patients with locally advanced or metastatic NSCLC who had classical and atypical sensitizing *EGFR* mutations. Tissue biopsies were obtained prior to the start of treatment and at or after disease progression; paired sample analyses were performed by NGS and mass spectrometry. In addition, the patients underwent assessments according to RECIST 1.1 every 8 weeks. ctDNA was also collected longitudinally; these results will be presented at a future meeting. The proportion of patients with a given tumor genetic and proteomic marker at the time of disease progression constituted the primary endpoint. ELIOS is the first prospective study with a primary objective of comparing paired tumor tissue biopsies taken pre-treatment and after RECIST progression.

A total of 154 patients received ≥ 1 dose of osimertinib. Among the 119 patients who experienced disease progression, 75 provided biopsies pairs, while only 46 of these were evaluable (i.e., primary analysis set). According to the authors, this highlights the challenges of obtaining post-progression tissue biopsies and emphasizes the need for more comprehensive non-invasive testing methods. Paired proteomics data were available for 6 patients (i.e., proteomic data set). At ESMO 2022, Piotrowska et al. reported the first interim analysis of the ELIOS trial [6].

Alterations & increased proteomic expression

At baseline, *TP53* mutations were the most common co-occurring mutations (74 %) in the primary analysis set, followed by *EGFR* amplifications (28 %) and *CDKN2A* loss (22 %). The prevalence of these alterations did not change significantly during the course of the study. With regard to the primary endpoint, **Table 2** lists the frequencies of major alterations at baseline and at progression. Evidence of sensitivity to later-line targeted therapies is present for *MET* amplification, C797S mutation, and *ALK* fusion. Amplification of the *NKX2-1* gene that codes for the TTF-1 protein was identified as a potential new resistance mechanism, although this requires further exploration and validation. Resistance mechanisms were well distributed between the different types

TABLE 2 Major genomic alterations at baseline and at the time of disease progression on first-line osimertinib

Gene alteration, n (%)	Baseline (n = 46)	Disease progression (n = 46)	Acquired (n = 46)	Evidence of sensitivity
MET amplification	2 (4)	9 (20)	8 (17)	√
CDKN2A deletion	10 (22)	11 (24)	7 (15)	
CDKN2B deletion	9 (20)	11 (24)	7 (15)	
MTAP deletion	7 (15)	10 (22)	7 (15)	
EGFR C797S mutation	0 (0)	7 (15)	7 (15)	√
NKX2-1 amplification	4 (9)	9 (20)	5 (11)	
EGFR amplification	13 (28)	11 (24)	5 (11)	
CCNE1 amplification	3 (7)	6 (13)	3 (7)	
ARAF amplification	0 (0)	2 (4)	2 (4)	
ALK fusion	0 (0)	1 (2)	1 (2)	√

of sensitizing mutations and were largely mutually exclusive.

The analysis of 15 selected markers from the proteomic data set revealed increased proteomic expression of the AXL and MET proteins by 67 % and 50 %, respectively, relative to baseline. No changes were observed for HER3 protein expression. Mass spectrometry confirmed higher AXL and MET expression at the time of progression, and upregulation of these markers in a subset of progressing tumors was consistent with prior data describing their role in acquired resistance to EGFR TKIs [7, 8]. Overall, the most prevalent acquired resistance mechanisms to osimertinib were *MET* amplification and overexpression, as well as *EGFR* C797S mutation. This was consistent with previous data [9-11]. Retrospective analyses on histologic transformation are ongoing, and molecular data are being collected for the remaining patients in the ELIOS trial.

INSIGHT 2: tepotinib/osimertinib

MET-amplification–mediated resistance against osimertinib is associated with a poor prognosis [12, 13]. In this setting with a high unmet need, combinations of the MET inhibitor tepotinib with the EGFR TKIs gefitinib and osimertinib have shown clinical activity in the INSIGHT study and the real-world setting, respectively [14, 15]. The global, open-label, phase II INSIGHT 2 trial is assessing the combination of tepotinib and osimertinib in patients with *EGFR*-mutated NSCLC and acquired resistance to first-line osimertinib in whom *MET* amplification has been detected by either central or local FISH testing of tissue biopsy (TBx), or central NGS testing of liquid biopsy (LBx). The second arm of the trial is receiving tepotinib monotherapy. Patients with stable, treated brain metastases are allowed to participate. *MET* amplification was defined as *MET* gene copy number (GCN) ≥ 5 and/or *MET/CEP7* ratio ≥ 2 according to TBx FISH and/or *MET* GCN ≥ 2.3 (Archer®) according to LBx NGS. The primary endpoint is the ORR by independent review for tepotinib/osimertinib-treated patients with *MET* amplification centrally confirmed by TBx FISH.

Among 425 pre-screened patients, *MET* amplification was detected in 153 patients (36 %). Most of them were identified by TBx FISH **(Figure 2)**. The primary analysis of INSIGHT 2 will be reported when all patients have ≥ 9 months of follow-up. At ESMO 2022, Mazières et al. presented initial results [16]. In the combination arm, 48 and 22 patients had a median follow-up of ≥ 3 and ≥ 9 months, respectively. Twelve patients in the tepotinib monotherapy arm had been followed for ≥ 6 months.

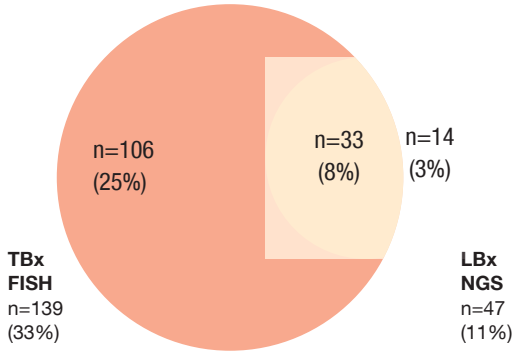

Figure 2: Proportions of patients with *MET* amplification detected by tissue-based (TBx) FISH and liquid-biopsy–based (LBx) NGS

Superiority of the combination approach

In the tepotinib/osimertinib-treated group with centrally confirmed *MET* amplification according to TBx FISH and ≥ 9 months of follow-up, the confirmed ORR by independent review was 54.5 %. A comparable rate of 45.8 % was observed for patients with ≥ 3 months of follow-up. For patients whose *MET* amplification status was based on LBx NGS, the ORRs were 50.0% and 56.5 % after a follow-up of ≥ 9 months and ≥ 3 months, respectively. Similar ORRs were reported according to *MET* amplification GCN (51.9 % and 40.0 % for ≥ 10 GCN and 5 to ≤ 10 GCN, respectively). Single-agent tepotinib, on the other hand, gave rise to an ORR of only 8.3 %.

The vast majority of patients experienced tumor shrinkage with tepotinib and osimertinib. Patients with brain metastases (n = 22) responded as well. Responses mostly occurred within 6 weeks and were observed regardless of the GCN cutoff. Median DoR had not been reached at the time of the analysis. The safety profile of the combination was consistent with the known profiles of tepotinib and osimertinib. AEs led to dose reductions in 18.2 %, and 6.8 % of patients discontinued treatment, primarily due to AEs.

In their summary, the authors noted that tepotinib plus osimertinib showed promising activity in patients with *EGFR*-mutant NSCLC and *MET* amplifications centrally confirmed by TBx FISH who progressed on first-line osimertinib, thus providing a potential chemotherapy-sparing targeted option in this setting. In addition, FISH *MET* GCN of ≥ 5 and/or a *MET/CEP7* ratio of ≥ 2 in TBx samples appeared to define a population that derives clinical benefit from the combination.

T-DXd: DESTINY-Lung02

The HER2-directed antibody-drug conjugate trastuzumab deruxtecan (T-DXd) has shown strong and durable clinical activity in patients with pretreated *HER2*-mutant NSCLC in the DESTINY-Lung01 study [17]. As these results warranted evaluation of the benefit/risk profile of T-DXd 5.4 mg/kg and further assessment of T-DXd 6.4 mg/kg, the randomized, phase II DESTINY-Lung02 trial is investigating these two doses in patients with metastatic *HER2*-mutant NSCLC after ≥ 1 treatment line including platinum-based chemotherapy. DESTINY-Lung02 is not powered to statistically compare the two arms. The confirmed ORR by blinded independent review constitutes the primary outcome. Findings from the prespecified early cohort (i.e., patients randomized ≥ 4.5 months before the interim analysis data cutoff) were presented at ESMO 2022 [18]. In this group, 52 and 28 patients received T-DXd 5.4 mg/kg and T-DXd 6.4 mg/kg, respectively. The safety analysis set included the total study population comprising 101 and 50 patients in the two arms.

T-DXd 5.4 mg/kg induced clinically meaningful responses, with an ORR of 53.8 % and a disease control rate of 90.4 %. As the median DoR had not been reached

yet, an additional 90-day follow-up response analysis was conducted that yielded a median DoR of 8.7 months. The ORR had risen to 57.7 % after the longer follow-up, thus continuing to demonstrate strong and clinically meaningful antitumor activity. For T-DXd 6.4 mg/kg, the ORR and the disease control rate were 42.9 % and 92.9 %, respectively, and median DoR was 5.9 months **(Table 3)**. Mean tumor size reductions amounted to -38.6 % and -34.6 % for the 5.4 mg/kg and 6.4 mg/kg doses, respectively.

The safety profile at both doses was consistent with the established safety profile of T-DXd, although the 5.4 kg/mg dose conferred lower rates of drug-related treatment-emergent AEs that were grade ≥3 (31.7 % vs. 58.0 %) or associated with drug discontinuation (7.9 % vs. 16.0 %), dose reduction (9.9 % vs. 26.0 %), drug interruption (13.9 % vs. 30.0 %), and death (1.0 % vs. 2.0 %). Any-grade adjudicated drug-related interstitial lung disease rates favored the lower T-DXd dose (5.9 % vs. 14.0 %). Most cases were rated as grade 1 or 2, and 50 % had resolved at the time of the analysis. As the authors noted, the entire evidence and the compelling positive benefit-risk balance support T-DXd 5.4 mg/kg as a new standard of care in patients with pretreated *HER2*-mutant NSCLC. Interstitial lung disease/pneumonitis remains an important identified risk, with effective early detection and management being critical in reducing the severity of this complication.

TABLE 3 **DESTINY-Lung02: response rates for T-DXd 5.4 mg/kg and 6.4 mg/kg in the prespecified early cohort**

Response assessment by blinded independent central review	T-DXd 5.4 mg/kg n = 52	T-DXd 6.4 mg/kg n = 28
Confirmed overall response rate, n (%)	28 (53.8)	12 (42.9)
Best overall response, n (%)		
Complete response	1 (1.9)	1 (3.6)
Partial response	27 (51.9)	11 (39.3)
Stable disease	19 (36.5)	14 (50.0)
Progressive disease	2 (3.8)	1 (3.6)
Not evaluable	3 (5.8)	1 (3.6)
Disease control rate, n (%)	47 (90.4)	26 (92.9)
Median duration of response, months	Not estimable	5.9
Median time to initial response, months	1.4	1.4
Median follow-up, months	5.6	5.4

Nintedanib/docetaxel after chemo-IO

Tumor angiogenesis is involved in the development of resistance to immune checkpoint inhibitors by promoting an immunosuppressive tumor microenvironment [19]. Angiogenesis-targeted agents are hypothesized to support the development of a pro-immunogenic microenvironment by the so-called angio-immunogenic switch [19, 20], thus reversing acquired resistance to immunotherapy. Cohort C of the prospective, non-interventional VARGADO study assessed the second-line use of the angiokinase inhibitor nintedanib plus docetaxel in patients with advanced adenocarcinoma of the lung who had progressed on first-line chemotherapy plus immunotherapy in routine clinical practice at centers in Germany. The analysis reported at ESMO examined treatment outcomes according to patient response to first-line therapy and ECOG performance status (PS) at baseline [21]. The best responses to chemotherapy/immunotherapy had been partial response (PR) and stable disease (SD) in 37.8 % and 25.9 % of patients, respectively, with 34.1 % progressing.

In 176 patients, the ORR associated with the combination was 35.0 %, and disease control resulted in 68.3 %. Median PFS and OS were 4.8 and 8.1 months, respectively. Among response-evaluable individuals, the ORR with nintedanib/docetaxel was improved in patients who had experienced PR or SD as best response to their first-line therapy (40.0 %) versus those who had developed disease progression (28.6 %). The same applied to the disease control rate (73.3 % vs. 62.9 %). Therefore, the best response to first-line treatment might be a surrogate marker for the clinical benefit of second-line nintedanib/docetaxel.

Another potential surrogate marker is the ECOG PS, as especially patients with PS 0-1 showed an association between the OS benefit observed in the second line and PR as best response to first-line therapy. In this group, median OS was 11.2 months. No clear differences emerged regarding PFS and best response to first-line treatment. The findings warrant further evaluation of the effect of these parameters on second-line treatment outcomes after chemoimmunotherapy. Taken together, these data support second-line nintedanib plus docetaxel as an effective treatment option following first-line checkpoint inhibitor combination therapy. ■

REFERENCES

1 Skoulidis F et al., Sotorasib for lung cancers with *KRAS* p.G12C mutation. N Engl J Med 2021; 384: 2371-2381
2 Johnson ML et al., Sotorasib versus docetaxel for previously treated non-small cell lung cancer with *KRAS* G12 mutation: CodeBreaK 200 phase 3 study. ESMO 2022, abstract LBA10
3 Remon J et al., Osimertinib treatment based on plasma T790M monitoring in patients with *EGFR*-mutant advanced non-small cell lung cancer: EORTC Lung Cancer Group 1613 APPLE phase II randomized clinical trial. ESMO 2022, abstract LBA51
4 Planchard D et al., Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Suppl 4): iv192-iv237
5 Leonetti A et al., Resistance mechanisms to osimertinib in *EGFR*-mutated non-small cell lung cancer. Br J Cancer 2019; 121(9): 725-737
6 Piotrowska Z et al., ELIOS: a multicentre, molecular profiling study of patients with EGFRm advanced NSCLC treated with first-line osimertinib. ESMO 2022, abstract LBA53
7 Wang F et al., Blockade of AXL activation overcomes acquired resistance to EGFR tyrosine kinase inhibition in non-small cell lung cancer. Transl Cancer Res 2019; 8(6): 2425-2438
8 Piotrowska Z et al., MET amplification as a resistance mechanism to osimertinib. J Clin Oncol 35, 2017 (suppl; abstr 9020)
9 Hartmaier RJ et al., Tumor genomics in patients with advanced epidermal growth factor receptor mutant non-small cell lung cancer whose disease has progressed on first-line osimertinib therapy in the phase II ORCHARD study. Cancer Res 2022; 82(Suppl 12): LB078
10 Ramalingam SS et al., Mechanisms of acquired resistance to first-line osimertinib:

preliminary data from the phase III FLAURA study. ESMO Congress 2018, abstract 5005
11 Ahn MJ et al., MET biomarker-based preliminary efficacy analysis in SAVANNAH: savolitinib+osimertinib in EGFRm NSCLC post-osimertinib. WCLC 2022, EP08.02-140
12 Wang Y et al., Clinical analysis by next-generation sequencing for NSCLC patients with MET amplification resistant to osimertinib. Lung Cancer 2018; 118: 105-110
13 Koulouris A et al., Resistance to TKIs in *EGFR*-mutated non-small cell lung cancer: from mechanisms to new therapeutic strategies. Cancers 2022; 14(14): 3337
14 Wu YL et al., Tepotinib plus gefitinib in patients with *EGFR*-mutant non-small-cell lung cancer with MET overexpression or MET amplification and acquired resistance to previous EGFR inhibitor (INSIGHT study): an open-label, phase 1b/2, multicentre, randomised trial. Lancet Respir Med 2020; 8(11): 1132-1143
15 Le X et al., Tepotinib with an EGFR-tyrosine kinase inhibitor in patients with EGFR-mutant MET-amplified NSCLC: A Case series. WCLC 2022, EP08.02-162
16 Mazières J et al., Tepotinib + osimertinib for EGFRm NSCLC with MET amplification after progression on first-line osimertinib: initial results from the INSIGHT 2 study. ESMO 2022, abstract LBA52
17 Nakada T et al., The latest research and development into the antibody-drug conjugate, [fam-] trastuzumab deruxtecan (DS-8201a), for HER2 cancer therapy. Chem Pharm Bull (Tokyo) 2019; 67(3): 173-185
18 Goto K et al., Trastuzumab deruxtecan in patients with *HER2* mutant metastatic non-small-cell lung cancer: interim results from the phase 2 DESTINY-Lung02 trial. ESMO 2022, abstract LBA55
19 Popat S et al., Anti-angiogenic agents in the age of resistance to immune checkpoint inhibitors: Do they have a role in non-oncogene-addicted non-small cell lung cancer? Lung Cancer 2020; 144: 76-84
20 Fukumura D et al., Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol 2018; 15(5): 325-340
21 Grohé C et al., Effect of best response to first-line treatment on outcomes with second-line nintedanib + docetaxel for patients with lung adenocarcinoma after first-line immune checkpoint inhibitor/chemotherapy combination therapy. ESMO 2022, abstract 1143P

Updates on immunotherapy-based treatment of stage III/IV disease

IPSOS: atezolizumab in platinum-ineligible patients

At least 40 % of patients with NSCLC have poor performance status (ECOG PS ≥ 2) and/or are elderly with multiple comorbidities and poor tolerance of treatment [1]. They frequently receive single-agent chemotherapy or best supportive care as they are often deemed ineligible for first-line platinum-based regimens. Usually, they are excluded from clinical trials conducted in the first-line setting. This population represents an important, under-studied group with an unmet medical need.

Therefore, the global, open-label, randomized, controlled, phase III IPSOS study assessed atezolizumab 1,200 mg Q3W (n = 302) compared to single-agent chemotherapy (vinorelbine or gemcitabine; n = 151) in treatment-naïve patients with stage IIIB/IV NSCLC who were considered unsuitable for first-line platinum-doublet chemotherapy. This was due to either ECOG PS 2/3 or PS 0/1 combined with advanced age (≥ 70 years) and substantial comorbidities or other contraindications to platinum chemotherapy. IPSOS was conducted at 91 sites in 23 countries. Most patients had ECOG PS 2, and approximately one third was ≥ 80 years old. Overall survival (OS) constituted the primary endpoint.

According to the analysis presented at ESMO 2022, first-line atezolizumab significantly improved OS over single-agent chemotherapy (10.3 vs. 9.2 months; HR, 0.78; p = 0.028; **Figure 1**) after a median follow-up of 41 months [2]. At 24 months, the proportion of patients alive was almost doubled in the experimental arm (24.3 % vs. 12.4 %). The superiority of the immune-based approach held true irrespective of PD-L1 status, histology, ECOG PS and other factors. Atezolizumab treatment gave rise to a higher objective response rate (ORR; 16.9 % vs. 7.9 %) and longer duration of response (14.0 vs. 7.8 months), while disease control was achieved in both arms to a comparable extent (57.3 % vs. 56.3 %). In the atezolizumab-treated arm, 4 patients (1.3 %) achieved complete responses (vs. 0 %). For progression-free survival (PFS), the analysis showed no difference (4.2 vs. 4.0 months; HR, 0.87), although there was a numerically higher risk reduction at 24 months (8.9 % vs. 1.6 %).

AEs and QoL outcomes

Treatment duration was nearly twice as long in the experimental arm (3.5 months for atezolizumab vs. 2.3 and 1.8 months for gemcitabine and vinorelbine, respectively). Nevertheless, fewer treatment-related grade 3/4 adverse events (AEs) occurred in the atezolizumab-treated population than in the chemotherapy group (16.3 % vs. 33.3 %). The same applied to treatment-related serious AEs (11.7 % vs. 15.6 %) and treatment-related grade 5 AEs (1.0 % vs.

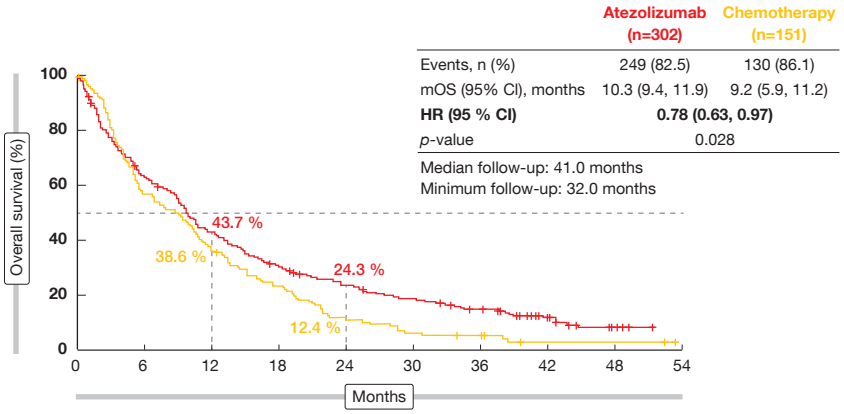

Figure 1: IPSOS: overall survival improvement with atezolizumab vs. single-agent chemotherapy in patients ineligible for platinum-based first-line chemotherapy

2.7 %). AEs led to discontinuation in 13 % in both arms; the low rate indicated that the treatments were well tolerated. No new or unexpected AEs of special interest were observed with atezolizumab.

Prespecified patient-reported outcomes were assessed using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. According to this, atezolizumab was associated with stabilization across all health-related quality of life functioning domains (i.e., role function, social function, cognitive function), while the chemotherapy arm showed some deterioration. Cough, appetite and chest pain improved in the experimental arm. On the other hand, patients in the control arm experienced deterioration regarding peripheral neuropathy, alopecia, and appetite. Time to confirmed deterioration was significantly longer with atezolizumab with respect to chest pain (HR, 0.51). As the authors noted in their summary, IPSOS is the first randomized study to demonstrate that first-line treatment with atezolizumab improves OS in this poor-prognosis population without driver mutations regardless of histology, PD-L1 status and ECOG PS while maintaining quality of life.

Dual PD-1/CTLA-4 inhibition: MEDI5752

MEDI5752 is a PD-1/CTLA-4 bispecific monoclonal antibody that fully binds PD-1 while preferentially binding CTLA-4 on PD-1–positive activated T cells, with the potential to improve efficacy and remain clinically tolerable [3]. A phase IB/II signal-finding study explored MEDI5752 in treatment-naïve patients with non-squamous NSCLC. The study contained a single-arm cohort testing 4 doses of MEDI5752 750 mg plus chemotherapy Q3W (n = 64) and a randomized part; here, the patients received either 4 doses of MEDI5752 1,500 mg plus chemotherapy Q3W (n = 20) or 4 doses of pembrolizumab 200 mg plus chemotherapy Q3W. Results from 91 patients were presented at ESMO 2022 by Ahn et al. [4]. The analyzed group included 41 patients in the randomized cohorts (20 and 21 in the experimental and control arms, respectively) and the first 50 patients in the single-arm cohort who had ≥ 8 weeks of follow-up.

MEDI5752 1,500 mg plus chemotherapy, as compared to pembrolizumab plus chemotherapy, induced numerical prolongation of OS (not reached vs. 16.5 months) and PFS (15.1 vs. 8.9 months). The ORRs were similar in the two arms (50.0 % vs. 47.6 %), although duration of response was doubled (20.5 vs. 9.9 months). In the PD-L1–negative group, 55.6 % vs. 30.0 % of patients responded.

Results obtained in the single-arm cohort that received MEDI5752 750 mg plus chemotherapy indicated encouraging efficacy, with 49 % of patients achieving ≥ 30 % reductions in target lesions and an ORR of 40.8 %. The PD-L1–negative cohort experienced ≥ 30 % reductions in target lesions in 55.6 % and responded in 44.4 %. Longer follow-up is required to assess response duration, PFS and OS in the single-agent group.

According to a translational analysis, MEDI5752 750 mg or 1,500 mg plus chemotherapy gave rise to higher peripheral CD4-positive T cell proliferation and clonal expansion than pembrolizumab plus chemotherapy. Tolerability of MEDI5752 750 mg plus chemotherapy was improved compared to MEDI5752 1,500 mg plus chemotherapy regarding rates of grade 3/4 treatment-related AEs (50 % vs. 80 %), ALT increases (all grades, 10 % vs. 55 %), and AEs leading to treatment discontinuation (20 % vs. 70 %). The authors concluded that MEDI5752 provides a potential option to improve upon standard of care in the first-line setting, especially in patients with PD-L1–negative NSCLC.

Nivo/ipi: what is the ideal treatment duration?

Limits for the duration of immunotherapy have been set arbitrarily without any firm evidence. At the same time, < 20 % of patients received 2 years of treatment in most of the randomized studies. In the phase III KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, KEYNOTE-407 and CheckMate 227 trials, this proportion was 15.3 % [5-9]. CheckMate 227 that explored first-line nivolumab/ipilimumab showed that responses lasted for ≥ 2 years in 47 % of responders, while only 8-12 % of patients were still on treatment at 24 months. At 2 years, the PFS rate was 20 %.

The question arose whether the duration of immunotherapy treatment could be shortened without altering long-term survival in patients who have achieved disease control, particularly with a view to reducing financial toxicity and avoiding late immune-related AEs that are potentially threatening. In the randomized, phase III, non-inferiority DICIPLE trial, patients with stage IV NSCLC who had achieved disease control after 6 months of treatment with nivolumab/ipilimumab were randomized to either observation (stop & go arm) or continuation of the same regimen (continuation arm). Patients who progressed in the stop & go arm received nivolumab/ipilimumab again, whereas platinum-based doublet chemotherapy was recommended upon progression in the continuation arm. Zalcman et al. reported the first results of the DICIPLE study at ESMO 2022 [10]. The two arms included 35 and 36 patients, respectively.

The trial was interrupted as the combination treatment will not be registered or reimbursed in Europe. Therefore, statistically sound conclusions are impossible, although with more than 25 months of follow-up, no signal emerged of any detrimental effect of stopping immunotherapy

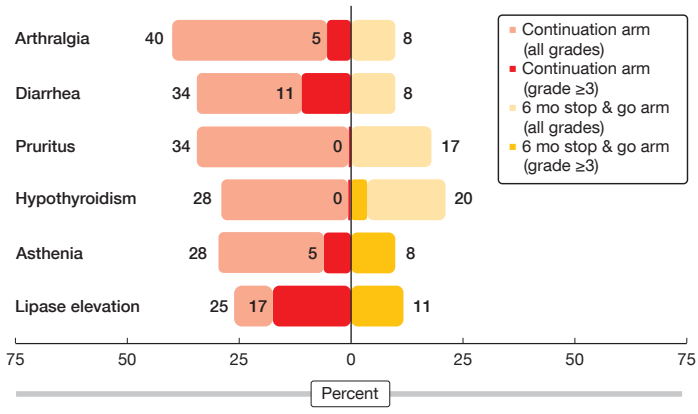

Figure 2: Continuation of nivolumab/ipilimumab after achievement of disease control vs. observation in stage IV NSCLC: most frequent adverse events post-randomization

at 6 months with respect to both PFS (35.2 vs. 20.8 months for stop & go and continuation, respectively) and OS (not reached in either arm) despite the low numbers. At 18 months, 93.7 % vs. 79.3 % of patients were alive (p = 0.33). The 12-month PFS rates were 81.2 % vs. 55.6 %.

In addition, the stop & go strategy conferred numerically less grade 3/4 immune-related AEs by a factor of 10 (2.9 % vs. 28.6 %) and less serious grade 3/4 AEs (11.8 % vs. 25.7 %). All of the most frequent AEs showed diminished rates in the experimental arm **(Figure 2)**. No patient died due to immune-related events. As the authors noted, these observations are only hypothesis-generating. Therefore, the phase II/III, randomized DIAL study has been launched with a similar design including induction treatment that contains platinum-based chemotherapy plus pembrolizumab (NCT05255302).

Three-year update of EMPOWER-Lung 1

Single-agent treatment with the anti-PD-1 antibody cemiplimab was compared to 4–6 cycles of chemotherapy in the global, randomized, phase III EMPOWER-Lung 1 trial conducted in patients with untreated advanced NSCLC and PD-L1 ≥ 50 %. The PD-L1 ≥ 50 % population included more than 560 individuals randomized in a 1:1 manner. Overall, 138 sites in 24 countries participated in EMPOWER-Lung 1. After 30 months of follow-up, cemiplimab gave rise to significant prolongation of PFS (8.2 vs. 5.7 months; HR, 0.54; p < 0.0001) and OS (not reached vs. 14.2 months; HR, 0.57; p = 0.0002) [11].

The 3-year survival analysis presented at ESMO 2022 corroborated the initial results [12]. Cemiplimab, as compared to chemotherapy, led to further improvement of PFS (8.1 vs. 5.3 months; HR, 0.51; p = 0.0001) in the PD-L1 ≥ 50 % population. Meanwhile, median OS had been reached in the experimental arm, and the relative risk reduction was again 43 % (26.1 vs. 13.3 months; HR, 0.57; p = 0.0001). The OS benefit was obtained in spite of a 75 % crossover rate. Furthermore, checkpoint inhibition gave rise to higher ORR (46.5 % vs. 21.0 %; OR, 3.264; p < 0.0001), with complete remissions in 8.1 % vs. 2.1 % and considerably longer duration of response (23.6 vs. 5.9 months). The safety profile of the treatment after the extended follow-up was consistent with the known data.

Continued cemiplimab and chemo beyond progression

The study included optional continuation of cemiplimab plus 4 cycles of chemotherapy upon progression in the experimental arm; this was defined as "treatment period 2" following "treatment period 1" that had taken place between randomization and disease progression. Continuation beyond progression was tested in light of the absence of optimal choices in patients progressing on checkpoint inhibition in whom the switch to chemotherapy is the current standard of care. It was hypothesized that chemotherapy might facilitate response to cemiplimab by increasing cancer cell immunogenicity or selectively depleting immunosuppressive cells [13-16]. In EMPOWER-Lung 1, 64 patients received ≥ 1 cycle of chemotherapy in addition to continued cemiplimab after progression.

The comparison between treatment period 1 and treatment period 2 revealed similar response rates (ORR, 29.7 % and 31.3 %, respectively). Whereas none of these patient had achieved complete response in period 1, this applied to 3 patients in period 2 (4.7 %). Median PFS was similar, at 6.2 and 6.6 months, respectively. The time between randomization and death in periods 1 and 2 combined was 27.4 months, with 15.1 months being due to continued treatment in period 2. Compared to historical data for second-line treatment with chemotherapy (OS, 8.4 months), continued cemiplimab with the addition of chemotherapy appeared to be superior [17]. The safety profile in these 64 patients was consistent with the established profile.

Taken together, continued cemiplimab beyond progression with the addition of chemotherapy provided meaningful and durable benefits. As the authors pointed out, this is the first such report from a phase III study. The results underline the importance of cemiplimab as first-line chemotherapy-free treatment for patients with advanced/metastatic NSCLC and PD-L1 ≥ 50 %.

KEYNOTE-189: long-term outcomes

The randomized, phase III KEYNOTE-189 trial has established the first-line treatment standard of pembrolizumab plus platinum/pemetrexed in non-squamous NSCLC without *EGFR/ALK* alterations. This regimen significantly improved OS and PFS compared with placebo plus chemotherapy [18]. Garassino et al. reported the 5-year update of KEYNOTE-189 after a median follow-up of 64.6 months [19]. The effective crossover rate on or off study was 57.3 %.

At 5 years, 19.4 % vs. 11.3 % of patients were alive, with median OS amounting to 22.0 vs. 10.6 months (HR, 0.60; **Figure 3**). The OS advantage was independent of PD-L1 expression and was also observed in the PD-L1–negative population. Likewise, superiority for PFS was maintained over the extended follow-up and despite the high crossover rate. Median PFS was 9.0 vs. 4.9 months, and the 5-year PFS rates were 7.5 % vs. 0.6 % (HR, 0.50). Again, the patients benefited from the addition of pembrolizumab irrespective of PD-L1 expression. In the total population, 48.3 % vs. 19.9 % of patients responded; the response rates were consistently higher in all PD-L1 subgroups.

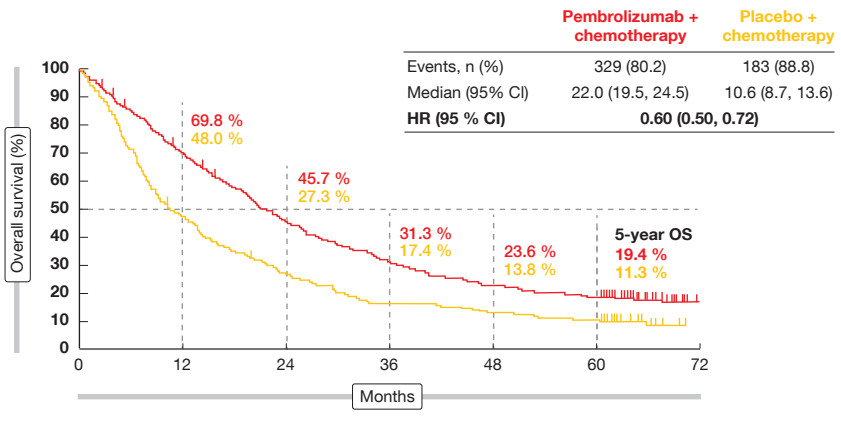

Figure 3: Long-term overall survival in the KEYNOTE-189 trial

New results have been obtained for 57 patients who completed 35 cycles of pembrolizumab treatment. In this cohort, the ORR was as high as 86.0 %, with 14.0 % and 71.9 % of patients achieving complete and partial responses, respectively. The median duration of response was 57.7 months. Three years after completion of the 35 pembrolizumab cycles, i.e., approximately 5 years from randomization, the OS rate was 71.9 %. Forty percent of patients were alive without disease progression or subsequent therapy. The long-term toxicity of the combined treatment proved manageable. Overall, these results continue to support first-line pembrolizumab plus platinum/pemetrexed as a standard of care in patients with metastatic non-squamous NSCLC without *EGFR/ALK* alterations.

Findings in KEYNOTE-407 after 57 months

In the setting of untreated, metastatic NSCLC with squamous histology, the phase III KEYNOTE-407 trial assessed the combination of pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel. This regimen significantly improved OS and PFS compared to placebo and chemotherapy [8, 20]. After a median follow-up of 56.9 months, the efficacy and safety update presented at ESMO 2022 demonstrated sustained improvements regardless of the effective crossover rate of 50.9 % [21]. The 5-year OS rates were 18.4 % vs. 9.7 % for pembrolizumab plus chemotherapy vs. chemotherapy alone, and median OS was 17.2 vs. 11.6 months (HR, 0.71). In the groups with PD-L1 TPS ≥ 50 % and 1 %-49 %, the combined approach improved OS (HRs, 0.68 and 0.61, respectively), while the PD-L1–negative population did not benefit from the addition of pembrolizumab (HR, 0.83).

Moreover, the PFS analysis revealed an advantage in the experimental arm (8.0 vs. 5.1 months; HR, 0.62), and the 5-year PFS rates were 10.8 % and 3.5 %, respectively. Risk reductions occurred in all PD-L1 categories, with HRs of 0.48, 0.60 and 0.70 for PD-L1 TPS ≥ 50 %, 1 %-49 %, and < 1 %, respectively. In the ITT population, 62.2 % vs. 38.8 % of patients responded; median duration of response was 9.0 vs. 4.9 months. Superior responses resulted with pembrolizumab-based treatment in all PD-L1 groups.

Fifty-five patients completed 35 cycles of pembrolizumab treatment. This cohort achieved an ORR of 90.9 %. The rates for complete and partial responses were 16.4 % and 74.5 %, respectively, and the median duration of response had not been reached yet. At 3 years after the completion of 35 cycles, 69.5 % of patients were alive, and 43.6 % had not experienced disease progression or subsequent therapy. The toxicity was manageable and consistent with prior reports. These long-term data continue to support pembrolizumab plus chemotherapy as a standard-of-care first-line treatment option for patients with metastatic squamous NSCLC.

POSEIDON: OS by histology and mutational status

Dual immune checkpoint inhibition with the anti-PD-L1 antibody durvalumab and the CTLA-4 inhibitor tremelimumab in addition to chemotherapy has demonstrated significant benefits for PFS (HR, 0.72; p = 0.0003) and OS (HR, 0.77; p = 0.0030) compared to platinum-based chemotherapy alone in untreated patients with metastatic NSCLC included in the global, randomized, open-label, phase III POSEIDON study [22]. Durvalumab alone plus chemotherapy, as compared to chemotherapy, also showed significant PFS prolongation (HR, 0.74; p = 0.0009) and a trend for OS improvement (HR, 0.86; p = 0.0758). In the triple combination arm of the three-arm study, durvalumab, tremelimumab and chemotherapy Q3W for 4 cycles was followed by durvalumab Q4W until disease progression plus a fifth dose of tremelimumab in week 16. In the arm that received 4 cycles of durvalumab plus chemotherapy Q3W, maintenance therapy included durvalumab Q4W until progression.

After a median follow-up of approximately 4 years, Johnson et al. reported the OS update including analyses by histology and *STK11, KEAP1* as well as *KRAS* mutational status [23]. The findings confirmed the durable long-term benefit of adding a limited course of tremelimumab to durvalumab and 4 cycles of chemotherapy, with median OS of 14.0 vs. 11.7 months in the chemotherapy-only arm and 48-month OS rates of 20.7 % vs. 8.3 % (HR, 0.75). For durvalumab plus chemotherapy vs. chemotherapy, this was 13.3 vs. 11.7 months (HR, 0.84). Data on serious AEs were collected after the final analysis for OS superiority; this analysis revealed no new safety signals.

Across the patient subgroups, the OS benefits were generally consistent with those in the ITT population. The addition of tremelimumab extended the sustained OS benefit to the cohort with PD-L1 < 1 %. Regarding histology, the survival advantage obtained with the triple com-

TABLE 1 **POSEIDON: overall survival outcomes in the three study arms according to *STK11, KEAP1* and *KRAS* mutation status**

	Durvalumab/ tremelimumab+ chemotherapy		Durvalumab + chemotherapy		Chemotherapy	
	STK11 mutation	*STK11* wildtype	*STK11* mutation	*STK11* wildtype	*STK11* mutation	*STK11* wildtype
OS, months	15.0	17.2	6.9	17.1	10.7	13.4
36-month OS rates, %	25.8	31.8	14.7	26.5	4.5	19.5
48-month OS rates, %	10.8	27.1	8.8	21.9	Not estimable	11.0
	KEAP1 mutation	*KEAP1* wildtype	*KEAP1* mutation	*KEAP1* wildtype	*KEAP1* mutation	*KEAP1* wildtype
OS, months	13.7	14.0	8.1	13.5	8.7	12.2
36-month OS rates, %	30.0	24.4	14.5	21.0	0.0	14.3
48-month OS rates, %	20.0	20.6	Not estimable	16.2	0.0	8.7
	KRAS mutation	*KRAS* wildtype	*KRAS* mutation	*KRAS* wildtype	*KRAS* mutation	*KRAS* wildtype
OS, months	25.7	17.1	12.6	17.1	10.4	14.4
36-month OS rates, %	40.0	27.1	26.1	23.7	15.8	18.5
48-month OS rates, %	32.9	21.3	23.2	17.7	10.8	10.0

bination was more pronounced in the group with non-squamous tumors; here, median OS was 17.2 vs. 13.1 months with chemotherapy, which translated into a 32 % risk reduction (HR, 0.68). At 48 months, 25.1 % vs. 10.0 % of patients were alive. The group with squamous histology showed median OS of 10.4 vs. 10.5 months, and the 48-month rates were 13.1 % vs. 5.5 % (HR, 0.83).

Patients with *STK11, KEAP1* or *KRAS* mutations represent a difficult-to-treat population. Consistent with an earlier analysis [24], a trend for sustained OS benefits with the triple combination vs. chemotherapy was observed in the groups with *STK11* (15.0 vs. 10.7 months; HR, 0.62), *KEAP1* (13.7 vs. 8.7 months; HR, 0.43), and *KRAS* mutation (25.7 vs. 10.4 months; HR, 0.55; **Table 1**). In their conclusion, the authors emphasized that these findings support the use of durvalumab plus tremelimumab and chemotherapy as a first-line strategy for patients with metastatic NSCLC, including harder-to-treat patient subgroups.

Ociperlimab & tislelizumab: AdvanTIG

Combinations of TIGIT and PD-1 inhibitors have shown promising antitumor activity in early studies conducted in patients with NSCLC [25-27]. The ongoing phase IB AdvanTIG-105 study is assessing the anti-TIGIT antibody ociperlimab 900 mg Q3W together with the PD-1 inhibitor tislelizumab 200 mg Q2W and chemotherapy in patients with metastatic squamous NSCLC (Cohort 1; n = 40) and metastatic non-squamous NSCLC (Cohort 2; n = 42). At ESMO 2022, Yu et al. presented results from these two cohorts in the dose-expansion part of the study [28].

Ociperlimab and tislelizumab in addition to chemotherapy demonstrated antitumor activity independent of histology. ORR, which constituted the primary endpoint, was 57.5 % and 54.8 % in Cohorts 1 and 2, respectively. Disease control was achieved in 90.0 % and 90.5 %, respectively. Median duration of response had not been reached yet in either cohort. The recommended phase II dose showed a manageable safety profile. Treatment-emergent AEs primarily included anemia (42.9 %), decreased neutrophil counts (39.3 %), and decreased leukocyte counts (36.9 %). Grade ≥ 3 treatment-related AEs occurred in 48.8 %, and immune-mediated AEs were reported in 53.6 %. No treatment-related AEs led to death.

Ociperlimab plus tislelizumab is already being investigated in the phase II and III settings. The randomized, phase II AdvanTIG-205 study is comparing the anti-TIGIT/anti-PD-1 combination plus chemotherapy with tislelizumab plus chemotherapy in untreated patients with locally advanced or recurrent NSCLC not eligible for curative surgery [29]. Similarly, the randomized, phase III AdvanTIG-302 study has been designed as a first-line trial; here, ociperlimab plus tislelizumab is tested against pembrolizumab (NCT04746924).

TABLE 2 **Clinical outcomes for tislelizumab vs. docetaxel in Asian and non-Asian patients observed in the RATIONALE-303 study**

Endpoint	Asian subgroup		Non-Asian subgroup	
	Tislelizumab (n = 424)	Docetaxel (n = 219)	Tislelizumab (n = 111)	Docetaxel (n = 51)
Overall survival, months	17.8	12.2	14.9	11.9
	HR, 0.65		HR, 0.73	
Progression-free survival, months	4.1	2.4	6.3	4.1
	HR, 0.62		HR, 0.67	
Objective response rate, %	21.5	5.9	27.0	11.8
Duration of response, months	13.8	4.2	10.3	6.1

Asians vs. non-Asians in RATIONALE-303

In the phase III RATONALE-303 study, single-agent tislelizumab has demonstrated significant clinical benefit compared to docetaxel in patients with advanced squamous or non-squamous NSCLC who had progressed during or after ≥ 1 platinum-containing regimen but had received no more than two prior lines of systemic chemotherapy [30]. The analysis of the Asian (n = 643) and non-Asian (n = 162) subgroups presented at ESMO 2022 revealed consistent efficacy across the endpoints for the entire population **(Table 2)** [31]. Moreover, tislelizumab was generally well tolerated in both subgroups. Fewer grade ≥ 3 treatment-emergent AEs (TEAEs) were reported in the experimental arm vs. the control arm for both Asians (41.1 % vs. 75.2 %) and non-Asians (45.9 % vs. 72.9 %). TEAEs leading to treatment discontinuation occurred in 10.6 % vs. 12.4 % of Asian patients and in 17.1 % vs. 16.7 % of non-Asian patients.

As many patients do not respond to PD-(L)1-targeted monotherapy or develop resistance after initial response [32], the phase III SAFFRON-301 trial is currently exploring the combination of tislelizumab with the TKI sitravatinib [33]. Sitravatinib has both immunomodulatory and antitumor properties due to its targeting TAM family receptors (TYRO3, AXL, MER) and VEGFR2/KIT [34-36]. Patients with unresectable locally advanced or metastatic NSCLC after ≤ 2 lines of systemic therapy are treated with either tislelizumab plus sitravatinib or docetaxel. Prior treatment must include platinum-based chemotherapy and an anti-PD-(L)1 antibody. OS and PFS are defined as the primary endpoints. ■

REFERENCES

1 Lilenbaum RC et al., Prevalence of poor performance status in lung cancer patients: implications for research. Thorac Oncol 2008; 3(2): 125-129

2 Lee SM et al., IPSOS: results from a phase 3 study of first-line atezolizumab vs single-agent chemotherapy in patients with NSCLC not eligible for a platinum-containing regimen. ESMO 2022, abstract LBA11

3 Dovedi SJ et al., Design and efficacy of a monovalent bispecific PD-1/CTLA4 antibody that enhances CTLA4 blockade on PD-1+ activated T cells. Cancer Discov 2021; 11(5): 1100-1117

4 Ahn MJ et al., MEDI5752 or pembrolizumab plus carboplatin/pemetrexed in treatment-naïve non-small-cell lung cancer: a phase 1b/2 trial. ESMO 2022, abstract LBA56

5 Reck et al., Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 2016; 375: 1823-1833

6 Mok TSK et al., Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-

small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019; 393(10183):1819-1830
7 Ghandi L et al., Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med 2018; 378: 2078-2092
8 Paz-Ares L et al., Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018; 379(21):2040-2051
9 Hellmann MD et al., Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. N Engl J Med 2019; 381: 2020-2031
10 Zalcman G et al., Nivolumab plus ipilimumab 6-month treatment versus continuation in patients with advanced non-small-cell lung cancer. ESMO 2022, abstract 972O
11 Sezer A et al., Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50 %: a multicentre, open-label, global phase 3 randomised controlled trial. Lancet 2021; 397(10274): 592-604
12 Özgüroglu M et al., Three-year survival outcome and continued cemiplimab beyond progression with the addition of chemotherapy for patients with advanced non-small cell lung cancer with PD-L1 ≥ 50 %: The EMPOWER-Lung 1 trial. ESMO 2022, abstract LBA54
13 Galluzzi L et al., Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell 2015; 28(6): 690-714
14 Bloy N et al., Immunogenic stress and death of cancer cells: contribution of antigenicity vs adjuvanticity to immunosurveillance. Immunol Rev 2017; 280(1): 165-174
15 Herbst RS et al., The biology and management of non-small cell lung cancer. Nature 2018; 553(7689): 446-454
16 Galluzzi L et al., Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. Nature Rev Clin Oncol 2020; 17: 725-741
17 Bersanelli et al., Chemotherapy in non-small cell lung cancer patients after prior immunotherapy: The multicenter retrospective CLARITY study. Lung Cancer 2020; 150: 123-131
18 Gandhi L et al., Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; 387(22): 2078-2092
19 Garassino MC et al., KEYNOTE-189 5-year update: first-line pembrolizumab + pemetrexed and platinum vs. placebo + pemetrexed and platinum for metastatic nonsquamous NSCLC. ESMO 2022, abstract 973MO
20 Paz-Ares L et al., A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE-407. J Thorac Oncol 2020; 15(10): 1657-1669
21 Novello S et al., 5-year update from KEYNOTE-407: pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer. ESMO 2022, abstract 974MO
22 Johnson M et al., Durvalumab ± tremelimumab + chemotherapy as first-line treatment for mNSCLC: results from the phase 3 POSEIDON study. J Thorac Oncol 2021; 16(10_suppl): S844
23 Johnson ML et al., Durvalumab ± tremelimumab + chemotherapy in 1L metastatic NSCLC: overall survival update form POSEIDON after median follow-up of approximately 4 years. ESMO 2022, LBA59
24 Peters S et al., Association between KRAS/STK11/KEAP1 mutations and outcomes in POSEIDON: durvalumab ± tremelimumab + chemotherapy in mNSCLC. WCLC 2022, OA15.04
25 Niu J et al., Safety and efficacy of vibostolimab, an anti-TIGIT antibody, plus pembrolizumab in patients with anti-PD-1/PD-L1-naïve NSCLC. Ann Oncol 2020; 31 (Suppl 4): S891-S892
26 Rodriguez-Abreu D et al., Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab plus atezolizumab versus placebo plus atezo as first-line treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). J Clin Oncol 2020; 38 (15_suppl): 9503
27 Ahn MJ et al., Vibostolimab, an anti-TIGIT antibody, as monotherapy and in combination with pembrolizumab in anti-PD-1/PD-L1-refractory NSCLC. Ann Oncol 2020; 31: S887
28 Yu Y et al., AdvanTIG-105: phase 1b dose-expansion study of ociperlimab + tislelizumab with chemotherapy in patients with metastatic squamous and nonsquamous non-small cell lung cancer. ESMO 2022, abstract 1017P
29 Zhu B et al., AdvanTIG-205: phase 2 trial of ociperlimab plus tislelizumab plus chemotherapy in first-line treatment of patients with locally advanced, unresectable, or metastatic non-small cell lung cancer. ESMO 2022, abstract 1194TiP
30 Zhou C et al., Tislelizumab versus docetaxel in previously treated advanced non-small cell lung cancer: final analysis of RATIONALE-303. WCLC 2022, EP08.01-014
31 Zhou C et al., Tislelizumab versus docetaxel as second- or third-line therapy in previously treated patients with advanced non-small cell lung cancer: Asian and non-Asian subgroup analysis of the RATIONALE-303 study. ESMO 2022, abstract 1031P
32 Xia L et al., PD-1/PD-L1 blockade therapy in advanced non-small-cell lung cancer: current status and future directions. Oncologist 2019; 24(Suppl 1): S31-S41
33 Zhou Q et al., SAFFRON-301: a phase 3 study of tislelizumab with sitravatinib versus chemotherapy in patients with locally advanced or metastatic non-small cell lung cancer previously treated with platinum-based chemotherapy and an anti-PD-1/PD-L1 antibody. ESMO 2022, abstract 1187TiP
34 Du W et al., Sitravatinib potentiates immune checkpoint blockade in refractory cancer models. JCI Insight 2018; 3(21): e124184
35 Percent IJ et al., Phase III trial of sitravatinib plus nivolumab vs. docetaxel for treatment of NSCLC after platinum-based chemotherapy and immunotherapy (SAPPHIRE). J Clin Oncol 2020; 38(15_suppl): TPS9635
36 Pircher A et al., Synergies of targeting tumor angiogenesis and immune checkpoints in non-small cell lung cancer and renal cell cancer: from basic concepts to clinical reality. Int J Mol Sci 2017; 18(11): 2291

Air-pollution–induced lung cancer: defining a targetable link

The close association between air pollution and increased lung cancer risk has been known for decades, although causation remained unknown. Lung cancer in never smokers is characterized by a low mutational burden and the absence of a carcinogen-induced DNA mutation signature. In general, evidence against the classical mutation model explaining tumor growth as a result of DNA mutations has emerged, thus raising the need for an alternative model. The model initially developed by Berenblum in 1947 states that for environmental carcinogens to cause cancer, promoters need to act on pre-existing potential driver mutations (i.e., initiators), thus leading to clonal outgrowth [1, 2].

The role of PM2.5

Atmospheric particulate matter with a diameter ≤ 2.5 µm (PM2.5) represents the smallest particles of air pollution and is a major risk factor for various diseases [3, 4]. In terms of global mortality contribution, PM2.5 equals tobacco. More than 99 % of the world's population live in areas where pollution exceeds the WHO-recommended PM2.5 threshold [5]. Five times more people are exposed to PM2.5 than to tobacco, although the relative risk is 15- to 20-fold lower than for smoking.

Swanton et al. found that the geographic distribution of *EGFR*-mutant lung cancer can be linked to PM2.5 concentrations, with a significant association between PM2.5 exposure and lung cancer incidence across the globe **(Figure)** [6]. This is an important observation as *EGFR*-mutant NSCLC occurs 4 to 5 times more frequently in never smokers than in smokers [7]. Based on three mouse models with pre-existing *EGFR* and *KRAS* mutations, the researchers demonstrated that air pollu-

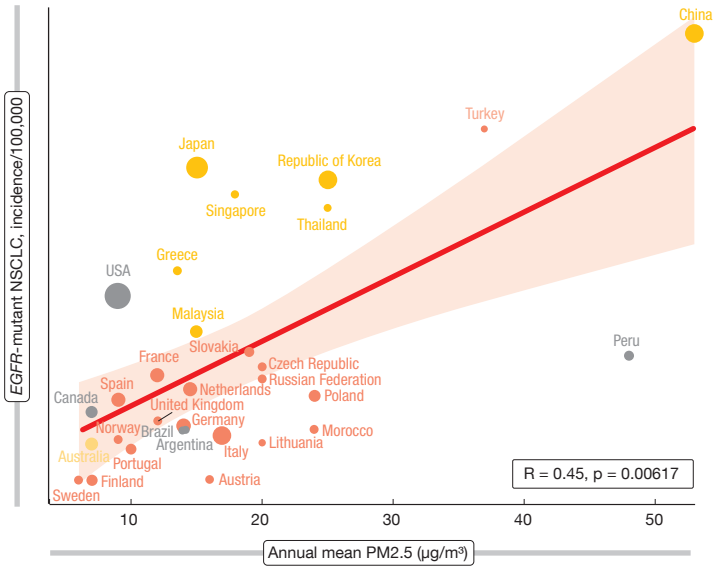

Figure: Association between the incidence of *EGFR*-mutant NSCLC and the annual mean PM2.5 concentrations (international data)

tion indeed promotes cancer. Dose-dependent increases in the numbers of tumors and adenoma-to-carcinoma transitions were observed independent of the underlying driver oncogene.

Promotion of a cancer-stem-cell–like state

With respect to the direct link between pollution and cancer, the researchers assessed the essential role of the alveolar type 2 (AT2) progenitor cell, which is the most common cell of origin for *EGFR*-mutant lung cancer. Inflammation, specifically IL-1β, promotes alveolar regeneration by mobilizing AT2 cells. IL-1β can induce a primed AT2 progenitor state [8]. In the mouse model, exposure to pollution gave rise to an AT2 progenitor state transcriptional signature, as well as increased influx of macrophages that release IL-1β. While neither air pollution nor the *EGFR* mutation alone appeared to be sufficient to augment a stem-cell state, stem cell capacity was shown to require both, with the *EGFR* mutation representing the initiator and pollution representing the promoter.

The role of inflammation for the pollution-induced tumor progenitor function was explored in the COPA study (NCT02236039) that included healthy never smokers who received either PM2.5 or filtered air for 2 hours, with the PM2.5 exposure levels being equivalent to those frequently encountered in major Asian cities. Bronchial brushing was taken 24 hours after exposure, and a transcriptomic analysis was performed via RNA sequencing. The results were compared with those obtained in mice. According to this, PM2.5 drove IL-1β release from lung epithelium and alveolar macrophages in both species. IL-1β actually mimicked PM2.5 in a stem cell progenitor assay. This fits with data from the CANTOS trial showing that the anti-IL-1β antibody canakinumab reduced lung cancer incidence and mortality [9]. In *EGFR*-mutant mice exposed to pollution, simultaneous anti-IL-1β antibody treatment completely abrogated the growth of tumors.

Mutations even in healthy tissue

An important prerequisite for the tumor promotion model developed by Berenblum is the presence of pre-existing mutations in latent cells. Indeed, studies of normal lung samples demonstrated that activating *EGFR* and *KRAS* mutations were present in 15 % and 53 %, respectively. These lung samples were obtained from never smokers, and it was found that cancer driver mutations increase with age.

Taken together, the results explain the absence of a mutagenic signature associated with pollution. IL-1β releases appear to act on mutant clones in histologically normal tissue harboring oncogenic mutations, leading to trans-differentiation to a progenitor stem-cell state that ultimately induces tumor formation. Thus, air pollution may promote cancer without directly causing DNA mutations.

These findings might facilitate molecular cancer prevention in high-risk populations. Moreover, other environmental carcinogens that do not mutate DNA might operate through similar, potentially actionable inflammatory pathways. Also, the question of whether UV light and tobacco act as both initiator and promoter raises concerns. These results provide a mandate to lower PM2.5 concentrations with the aim to improve long-term health outcomes in pollution-exposed populations. ■

REFERENCES

1 Berenblum I, Shubik P, A new, quantitative, approach to the study of the stages of chemical carcinogenesis in the mouse's skin. Br J Cancer 1947; 1(4): 383-391
2 Balmain A, The critical roles of somatic mutations and environmental tumor-promoting agents in cancer risk. Nat Genet 2020; 52(11): 1139-1143
3 Katsouyanni K et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 2001; 12: 521-531
4 Klemm RJ et al., The impact of frequency and duration of air quality monitoring: Atlanta, GA, data modeling of air pollution and mortality. J Air Waste Manag Assoc 2011; 61: 1281-1291
5 https://www.who.int/news/item/04-04-2022-billions-of-people-still-breathe-unhealthy-air-new-who-data
6 Swanton C et al., Mechanism of action and an actionable inflammatory axis for air pollution induced non-small cell lung cancer: Towards molecular cancer prevention. ESMO 2022, abstract LBA1
7 Mazières J et al., Specificities of lung adenocarcinoma in women who have never smoked. J Thorac Oncol 2013; 8(7): 923-929
8 Choi J et al., Inflammatory signals induce AT2 cell-derived damage-associated transient progenitors that mediate alveolar regeneration. Cell Stem Cell 2020; 27(3): 366-382.e7
9 Ridker PM et al., Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet 2017; 390(10105): 1833-1842

Benefits of lung cancer mass screening in China

The LUNG-CARE project presented by Liang et al. aimed to evaluate the outcome of mass lung cancer screening in a Chinese general population and to investigate risk factors to improve risk assessment for screening [1]. This was based on the consideration that screening should not be restricted to smokers in Asia as lung cancer in women and non-smokers is more common than in Europe and the United States. Between 2017 and 2021, residents of Guangzhou aged 40-74 years who accepted to undergo one-off low-dose computed tomography (LDCT) were eligible. Exclusion criteria comprised a diagnosis of lung cancer or treatment related to lung cancer within the past 5 years, previous chest CT within the past year and significant cancer-related symptoms such as hemoptysis and dyspnea. The primary objective was the prevalence of lung cancer in the general population of Guangzhou.

Mortality reduction by 63 %

A total of 12,644 individuals were assessed for eligibility, and 11,708 completed LDCT screening. Solid or subsolid nodules sized ≥ 5 mm or pure ground glass nodules ≥ 8 mm were detected in 2,245 persons, resulting in a detection rate of 19.2 %. Invasive diagnostic procedures including surgery followed in 230 cases. Overall, pathologically confirmed lung cancers were detected in 1.7 %, with 86.0 % of these patients staged as 0 or 1. The incidence of lung cancer increased with age and showed a peak in the group aged 60-64. At the same time, the proportion of stage 1 disease decreased. This was in line with previous results from a population level analysis [2].

Compared to the unscreened control group from the same community that comprised approximately 110,000 individuals, LDCT screening increased the survival probability of lung cancer patients, with a 63 % relative risk reduction (HR, 0.37; p < 0.001). This was much higher than the risk reduction observed in the China National Lung Cancer Screening program that had been conducted in individuals classified to be at high risk according to a sex-specific risk score (HR, 0.69) [3]. The authors attributed this difference to the inclusion of non–high-risk individuals. Lung cancer prognosis was consistently better in the screened group compared to the unscreened group, which was probably due to the higher proportion of patients with early-stage disease.

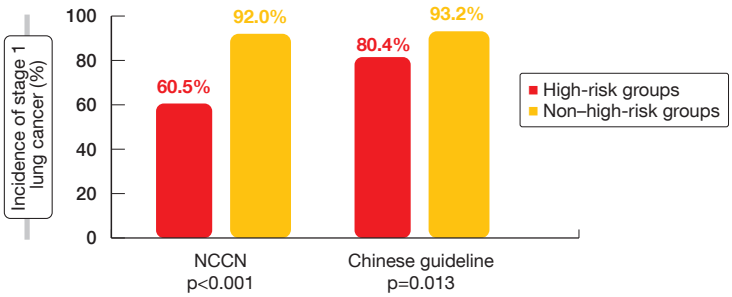

Figure: Incidence of stage 1 lung cancers in the screened population stratified by risk criteria according to the NCCN and Chinese guidelines

Cancer cases irrespective of established risk factors

Within the group of lung cancer patients identified by mass screening, only 19.6 % and 55.6 % met the high-risk criteria defined by the NCCN guideline and the Chinese guideline, respectively [4, 5]. Therefore, upfront restriction to the group with established high-risk features would have led to missing a large proportion of cases. Detection rates were similar across people defined as high-risk and non–high-risk according to the NCCN guideline (2.0 % vs. 1.6 %; p = 0.245). According to the Chinese guideline, the detection rate was higher in the high-risk group, although it was considerable even in the non–high-risk group (2.3 % vs. 1.3 %; p < 0.001). Moreover, surprisingly, stage 1 lung cancer occurred significantly more often in non–high-risk individuals than in the high-risk cohorts according to both guidelines **(Figure)**.

Using a Markov model, the scientists demonstrated that mass screening is cost-effective, with incremental cost effectiveness ratios averaging 14,002 $ per quality-adjusted life year. While the total cost of screening and the ensuing treatments amounted to 6.18 million $, the total benefit of this strategy was estimated at 36.5 million $.

In order to expand the current criteria, the authors identified risk factors that had been collected based on questionnaires. Multivariate analyses identified the following independent risk factors: personal cancer history, exposure to silicon dioxide, older age, food allergy, history of asthma, and family history of lung cancer. An integrated prediction model yielded an AUC of 0.71, which was higher than the AUCs for the criteria used in the NCCN and Chinese guidelines (0.52 and 0.62, respectively). The authors concluded that the risk assessment for lung cancer screening can be improved based on a risk prediction model including these characteristics combined with CEA that was also significantly elevated. ■

REFERENCES

1 Liang W et al., Community-based mass screening with low-dose CT for lung cancer in Guangzhou. ESMO 2022, abstract LB48
2 Li C et al., Optimal starting age for lung cancer screening with low-dose computed tomography: a population level analysis. J Thorac Oncol 2019; 14(4): e82-e84
3 Li N et al., One-off low-dose CT for lung cancer screening in China: a multicentre, population-based, prospective cohort study. Lancet Respir Med 2022; 10(4): 378-391
4 Wood D et al., NCCN Guidelines® Insights: Lung Cancer Screening, Version 1.2022. J Natl Compr Canc Netw 2022; 20(7): 754-764
5 Han B et al., Oncology Society of Chinese Medical Association guideline for clinical diagnosis and treatment of lung cancer (2021 edition). Zhonghua Zhong Liu Za Zhi 2021; 43(6): 591-621

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Expert interviews at ESMO 2022

Marina Garassino comments on checkpoint inhibition in lung cancer patients with oncogenic drivers, highlights novel developing therapies in EGFR-mutant NSCLC patients with resistance to TKIs, summarizes the most relevant findings presented at ESMO 2022 in terms of the management of patients with previously untreated, metastatic non-squamous and squamous NSCLC without EGFR/ALK alterations as well as patients with extensive-stage small-cell lung cancer; and finally discusses how artificial intelligence can be used to predict the efficacy of immunotherapy in lung cancer patients.

Noemi Reguart outlines if EGFR-directed treatment in the setting of advanced NSCLC should be based on T790M monitoring in clinical practice, outlines recent insights gained in the negative CANOPY-A trail using the anti-IL-1β antibody canakinumab after resection of early-stage NSCLC and summarizes the current treatment landscape in Europe with respect to small-cell lung cancer.

Gérard Zalcman discusses recent findings regarding the duration of immune checkpoint inhibitor treatment in patients with NSCLC, expectations of checkpoint inhibitor therapy in the setting of unresectable malignant pleural mesothelioma and how the treatment of patients with malignant pleural mesothelioma might be further optimized based on molecular findings.

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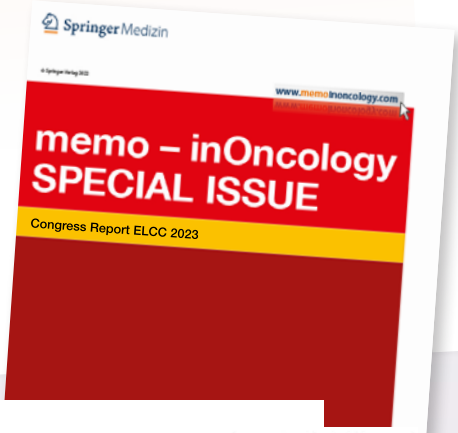
Stacey A. Cohen explains if ctDNA can detect MRD and predict recurrence in patients with colon cancer in a real-world setting, if it should be used in daily clinical practice or as a surveillance biomarker in stage II ctDNA-negative colon cancer patients. Moreover, she depicts how the treatment of patients with colon cancer might change in the foreseeable future.



Forthcoming Special Issue

This special issue will be offering a synopsis from the ELCC 2023 that will be held in March 2023. The report promises to make for stimulating reading, as the ELCC Congress itself draws on the input from a number of partner organizations, representing a multidiscplinary approach to lung cancer treatment and care. Stay tuned for the latest news in oncology and its subspecialties.

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